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THE TREATMENT OF GONORRHEAL AND RHEUMATOID ARTHRITIS WITH SULFANILAMIDE*

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THE reports to date[1, 2, 3] indicate that sulfanilamide is as effective as specific antiserum in the treatment of meningococcal infections. These results and the close biological relations between the meningococcus and the gonococcus have suggested to various workers[4–9] that sulfanilamide might have a similar effect on gonococcal infections. Because of the difficulties encountered in producing gonococcal infections in animals, experimental studies similar to those employed in determining the chemotherapeutic value of sulfanilamide in hemolytic streptococcal,[10–15] meningococcal[16] and pneumococcal[17, 18] infections have not been attempted. Therefore establishment of the efficacy of sulfanilamide therapy against gonococcal infections must be based on clinical results.

The results obtained by certain investigators[3, 4, 7, 8, 19–21] suggest that sulfanilamide is effective in treating uncomplicated gonococcal infections. The use of this drug in the treatment of gonorrheal arthritis, however, has been limited.[3, 5, 6, 9] Heretofore we have agreed with other workers[22–26] that artificially induced fever represents the nearest approach to a specific form of therapy for gonorrheal arthritis. We observed that fever therapy was satisfactory in arresting the arthritis in 80 patients, but noted that many of the associated genitourinary infections persisted. Because of the hazards of fever therapy and our inability to cure more regularly the genitourinary focus, we were led to investigate the effect of sulfanilamide§ on gonorrheal arthritis. Similar studies were made on patients suffering from rheumatoid arthritis in order to compare the results in an arthritis of unknown origin (rheumatoid arthritis) with those in one of known origin (gonorrheal arthritis). In order to be assured of the greatest possible number of cures, sulfanilamide was administered in most cases in large daily doses for several weeks. The results obtained and the various toxic manifestations — their significance and possible control — observed during and following this form of administration will be presented.

METHODS EMPLOYED

No case was included as proved gonorrheal arthritis unless the following criteria were satisfied: a history of gonorrheal infection; a history of joint disease consistent with gonorrheal arthritis; the isolation of gonococci from the genitourinary focus or synovial fluid. Probable gonorrheal arthritis was diagnosed when the first two requirements were met and the gonococcal complement-fixation test was positive. To date we have treated 18 cases of gonorrheal arthritis, of which 14 were proved and 4 probable.

One (Case 22) of the 10 cases of rheumatoid arthritis treated with sulfanilamide had an associated gonorrheal genitourinary infection. This patient gave a history of a progressive symmetrical arthritis antedating the onset of the gonococcal infection. Two cases (23 and 24) had a history of a previous urethritis. Both patients had chronic prostatitis and positive gonococcal complement-fixation tests. Gonococci were never isolated in either case. The gonococcal infection antedated the rheumatoid arthritis by two and seventeen years respectively.

Two cases of uncomplicated gonorrhea and 1 with an associated ischial bursitis have been included. They demonstrate the effect of sulfanilamide therapy on the genitourinary focus, as well as illustrate certain toxic manifestations which may be encountered.

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Roentgenograms were taken of all involved joints at the time of entry and prior to discharge, and oftener if indicated. Complete blood studies and urinalyses were made at frequent intervals during and following the administration of sulfanilamide. Serum nonprotein nitrogen determinations were usually made prior to and following treatment. Urine-concentration and divided phenolsulfonephthalein urine-excretion tests[27] were made before and after sulfanilamide therapy in a few cases. They were always carried out if there was any reason to suspect the existence of renal impairment. Bromsulfalein liver-function tests were carried out on a few patients prior to and following treatment. Serum-chloride,[28] carbon-dioxide combining power[29] and bilirubin determinations[30] were usually made at biweekly intervals. The sedimentation rates were determined frequently.[31] Free sulfanilamide determinations[32, 33] were made on serum or whole blood at frequent intervals in most cases.

Administration of Sulfanilamide

All patients were hospitalized. The sulfanilamide was administered by mouth except in Case 1, in which an initial dose of 90 cc. of 2.5 per cent Prontosil solution was given intramuscularly. Large doses were employed in all cases unless the drug caused marked gastric or toxic symptoms. In that event it was reduced to two thirds or half the original dose. The dose was calculated in the following manner: 3/4 gr. per pound of body weight or 1 gm. per 20 pounds of body weight, provided the total dose did not exceed 120 gr. or 8 gm. In some cases half the total calculated dose was administered initially and again in four hours. Then, in order to maintain a constant blood-sulfanilamide level, one sixth of the total calculated dose was given every four hours day and night. In most cases one sixth of the total calculated twenty-four hour amount was given every four hours, beginning with the initial dose. The latter method did not enable us to maintain so high a blood-sulfanilamide level as is at times necessary. Most patients received such doses of the drug for two weeks or longer. In some cases half or one third the calculated daily dose was continued for another two weeks. In Case 2 the drug was administered in full doses for only one week and then discontinued. An equal dose of sodium bicarbonate was administered with each dose of sulfanilamide except in Cases 3, 15, 18, 21, 30 and 31. This practice seemed to lessen the gastric symptoms, and theoretically speaking is supposed to aid in counteracting the accompanying so-called acidosis.[34]

Clinical Results

Proved Gonorrheal Arthritis with Infected Synovial Fluids

Of the 14 cases having proved gonorrheal arthritis, the most significant results were obtained in Cases 1, 2 and 3. These presented extremely painful joints from which gonococci were isolated. This is the type of gonorrheal arthritis which if allowed to go untreated is very liable to end with considerable joint destruction and some permanent loss of function. In order to prove that sulfanilamide is a specific chemotherapeutic agent for gonorrheal arthritis, it must be demonstrated that this form of therapy arrests more promptly and effects a larger percentage of cures in severe gonorrheal arthritis with infected synovial fluids than do other forms of therapy. Conclusions based on the results obtained in the treatment of milder cases of gonorrheal arthritis are very apt to be erroneous, because the end results are very satisfactory in a large percentage of this group when nothing more than bed rest and good supportive treatment are employed. Because the results in Cases 1, 2 and 3 are so striking, the clinical records are presented in some detail.

Case 1. E. S., a 24-year-old, married Italian woman, entered the hospital with a diagnosis of rheumatic fever. Four weeks previously, following coitus, she had developed leukorrhea and dysuria. Four days later she had a severe shaking chill followed by a temperature of 104°F., headache and severe pain in the jaws, neck and lower back. The left knee became acutely swollen and painful 10 days prior to entry. (This knee had been injured 1 month before, but was considered normal just prior to the onset of the arthritis.) The patient had had acute rheumatic fever at the age of 9 without cardiac complications.

Physical examination was normal except for an extremely painful, red, swollen, flexed left knee joint containing an increased amount of synovial fluid, acute endocervicitis and profuse vaginal discharge. The knee was so painful that immobilization with a cast, opiates and analgesics were required. Gonococci were demonstrable in the aspirated synovial fluid and the cervical smears. The temperature for 3 days prior to treatment was 100 to 102°F. X-ray examination of the left knee was negative except for an effusion and swelling of the soft tissue.

Three days after entry the patient received 90 cc. of 2.5 per cent Prontosil solution intramuscularly. This was followed by 1 gm. of sulfanilamide plus the same amount of sodium bicarbonate every 4 hours day and night for 11 days. Twenty-four hours after the institution of sulfanilamide therapy, opiates and analgesics were no longer required. Forty-eight hours later the cast was removed. The knee then had 30 degrees of voluntary painless motion; 2 days later this had increased to 90 degrees. Within 2 weeks the knee was painless, motions were normal and weight-bearing was possible. There remained slight swelling in the region of the infrapatellar fat pad. As can be seen from Table 1, the synovial fluid became sterile on the 2nd day of therapy and the synovial-fluid leukocyte count fell from an initial level of 41,000 (98 per cent polymorphonuclears) to 1000 (6 per cent polymorphonuclears)

in 7 days. All pelvic smears obtained after the 1st day of treatment were negative for gonococci, and the fixation test never became positive (Table 2). The serum carbon-dioxide combining power never fell below 57.4 vol. per cent. The initial sedimentation rate was 1.69 mm. per minute; 3, 5 and 12 weeks later it was 0.79, 0.43 and 0.29 mm. respectively. The hematologic changes which occurred are presented in Table 3.

had developed acute pain, heat, redness and swelling of the right knee. Until entry she had received no medication other than morphine to control the intense pain. There was no history of other joint involvement, chills or fever. Her husband, who was being treated for gonorrhea, also developed acute pain and swelling in his feet 4 days after the onset of her arthritis.

Physical examination was essentially normal except for

Table 1. *Changes Observed in Infected Synovial Fluids Following the Administration of Sulfanilamide.*

Case No. (Age and Sex)	Daily Dose of Sulfanilamide	Time in Relation to First Day of Therapy	Synovial Fluid Findings					
			Amount	Leukocytes	Polymorphonuclear Leukocytes	Sugar	Culture	Gonococcal Complement-Fixation Test
	gm.	*day*	*cc.*	*per cu. mm.*	*%*	*mg. %*		
1 (24 F)	7.5 (1st day) 6.0 (10 days)	Before	60	41,000	98	29.0	Positive	Negative
		After: 2nd	25	13,200	98	82.4	Negative	Negative
		7th	2	1,000	6	Not tested	Negative	Not made
2 (39 F)	7.0 (7 days)	Before	20	90,000	95	Trace	Positive	Positive
		After: 3rd	None					
		4th	0.5	Bloody	86	Not tested	Negative	Not made

Cyanosis was present throughout the period of therapy. The temperature which had been 102 to 105°F. from the 4th to the 11th day disappeared 24 hours after discontinuance of the drug. No other toxic symptoms were noted.

Summary. A patient with proved acute gonorrheal arthritis and endocervicitis responded promptly to large doses of sulfanilamide. She made a complete recovery

an intensely painful, red, swollen, effused right knee, edema of the right lower leg, profuse vaginal discharge, endocervicitis and pallor of the mucous membranes and skin. The knee was held in 5-degree flexion. The overlying skin was hot. Because of the intense pain the patient resisted any attempt to move the joint. Gonococci were demonstrated in the smears and cultures of the

Table 2. *Effect of Sulfanilamide Therapy on Genitourinary Foci of Gonococcal Infection.*

Case No.	Sex	Gonococci in Genitourinary Tract			Gonococcal Complement-Fixation Test on Serum			Time Followed	Remarks
		Before Treatment	After Third Day of Treatment	No. of Examinations	At Time of Entry	At Time of Discharge	At Time of Last Follow-up		
								wk.	
1	F	Yes	No	3	Negative	Negative	Negative	46	
2	F	No	No	3	Negative	Negative	Negative	7	
3	F	Yes	No	5	Negative	Negative	Negative	4	
4	F	Yes	No	3	Positive	Positive	Negative	48	
5	F	Yes	No	3	Positive	Positive	Negative	20	
6	F	Yes	No	4	Negative	Positive	Negative	8	
7	M	Yes	No	4	Positive	Positive	Positive	4	No urethral discharge after 2nd day of therapy.
8	M	Yes	No	3	Positive	Positive	Negative	12	No urethral discharge after 2nd day of therapy.
9	M	Yes	Yes	10	Positive	Positive	Positive	7	Gonococci still present after 7 gm. of sulfanilamide given each day for 7 days. Disappeared after increasing dose to 9.3 gm.
10	M	Yes	No	3	Positive	Positive	Positive	3	No urethral discharge after 2nd day of therapy.
11	M	Yes	No	4	Positive	Positive	Positive	3	No urethral discharge after 2nd day of therapy.
12	M	Yes	No	6	Positive	Positive	Negative	8	No urethral discharge after 1st day of therapy.
13	M	Yes	No	4	Negative	Positive	Negative	8	No urethral discharge after 2nd day of therapy.
14	M	Yes	Yes*	10	Positive	Positive	Positive	8	Genitourinary symptoms unaffected.
15	F	No	No	6	Positive	Positive	Positive	6	
16	F	No	No	4	Positive	Positive	Positive	28	
17	M	No	No	4	Positive	Positive	Positive	16	No genitourinary symptoms at onset of therapy.
18	F	No	No	3	Positive	Positive	Negative	44	
21	M	Yes	No	3	Positive	Positive	Negative	12	No urethral discharge after 2nd day of therapy.
22	M	Yes	No	4	Positive	Positive	Positive	4	No urethral discharge after 2nd day of therapy.
24	M	No	No	4	Positive	Positive	Negative	4	No genitourinary symptoms at onset of therapy.
27	F	Yes	No	3	Negative	Negative	Negative	8	
28	M	Yes	No	3	Negative	Negative	Negative	8	No urethral discharge after 2nd day of therapy.

*Subsequently, no gonococci demonstrable by culture or smear.

after 11 days of such therapy. During a 46-week follow-up period, she has remained well, all clinical examinations and laboratory tests being normal.

Case 2. A. S., a 39-year-old, married woman, entered the hospital with acute gonorrheal arthritis and endocervicitis. Five months previously she had noticed a profuse leukorrhea, frequency of urination, dysuria and nocturia. Three weeks prior to entry, after scrubbing the floor she

synovial fluid; none were ever found in repeated pelvic smears. The highest temperature recorded prior to treatment was 99.5°F. Roentgenograms showed considerable soft-tissue swelling and a joint effusion. There was moderate flecky decalcification of the femoral and tibial condyles. The medial surfaces of both the femur and the tibia showed areas of destruction.

Sulfanilamide therapy was begun on the day of entry.

Table 3. *Hematologic Variations Observed During Sulfanilamide Therapy.*

Case No. (Age and Sex)	Sulfanilamide (Total Dose)	Time in Relation to First Day of Therapy	Laboratory Data: Erythrocytes	Hemoglobin*	Leukocytes	Polymorphonuclear Leukocytes	Reticulocytes	Serum Bilirubin	Case Summary and Remarks
		day	× 10^6	%	× 10^3	%	%		
1 (24 F)	90 cc. (2.5%) Prontosil intramuscularly; then 66 gm. in 11 days.	Before	3.3	80	15.2	79	Not done	Not done	Eighth day, stained smears showed red cells filled with hemoglobin, a preponderance of macrocytes, a few microcytes, and immature erythrocytes. Forty-five per cent of polymorphonuclear leukocytes, young forms. Volume index 1.3, color index 1.2. Ninth and 16th days, 600-cc. blood transfusions.
		After:							
		8th	2.9	70	8.0	78			
		15th	3.9	80	7.0	76			
2 (39 F)	49 gm. in 7 days	Before	3.6	65	9.0	75			Ninth day, blood smear similar to Case 1. Thirteenth day, volume index 1.4, color index 1.4. Anemia not treated. No urobilinogen observed. Uneventful recovery.
		After:							
		7th	2.5				7		
		9th	2.2	50	28.6	80	12		
		12th	2.0	55	18.5	65	22	Normal	
		13th	1.8	55	12.0				
		20th	3.4	50	10.3	72	6		
3 (18 F)	79.2 gm. in 12 days	Before	4.7	90	10.7	79			Beginning on the 6th day, 1.02 gm. of ferrous sulfate given each day. Fourteenth day, blood smear similar to Case 1. Nineteenth day, volume index 1.4, color index 0.9. No urobilinogen observed. Fragility test normal.
		After:							
		14th	2.4	60	6.1	69	0.4	Normal	
		15th	2.4	70	7.6	68	9		
		16th	2.4	65	5.5	68	15		
		17th	2.6	60	5.3		20		
		18th	2.7	50	5.5		10		
		30th	3.4	70	5.8				
		34th	3.0	60	1.8	43	1		
		37th	3.3		4.0	48			
		38th	3.7	70	5.5				
4 (36 F)	130.6 gm. in 25 days	Before	4.0	70	10.6	70		Not done	Twenty-fifth day, blood smear showed reduction in percentage of polymorphonuclear leukocytes. No treatment for leukopenia. Volume index 1.1, color index 0.9.
		After:							
		25th	3.5	70	2.8				
		27th	3.4	68	2.8	50	3		
		33rd	3.7	75	7.2	50	1		
6 (27 F)	68.0 gm. in 18 days	Before	4.4	90	14.0	78	0		Eighteenth day, blood smear similar to Case 1. Color index, 1.2. Anemia not treated.
		After:							
		6th	3.8		9.0		4		
		9th	2.8		8.1		11	Normal	
		18th	2.4	60			10		
		26th	3.4	60					
9 (39 M)	100.3 gm. in 14 days	Before	5.1		14.2	79	2		Twenty-first day, blood smear similar to Case 1. Anemia not treated.
		After:							
		16th	4.0		14.5	73	0.5	Normal	
		21st	3.5		15.2	63	4		
		28th	4.1	80	8.2		4		
		47th	5.0	100	9.8				
10 (42 M)	259.3 gm. in 43 days	Before	4.9	82	12.2	82			Twenty-fourth day, blood smear similar to Case 1. Color index, 1.2. Forty-second day, 500-cc. blood transfusion.
		After:							
		28th	3.2	80	12.2	80			
		36th					4	Normal	
		40th	3.4	80			12		
		45th	5.1	80			4		
11 (32 M)	133.8 gm. in 25 days	Before	4.9	90	15.2	88	0		Twenty-second day, 10 per cent eosinophils; blood smear similar to Case 1. Anemia not treated.
		After:							
		25th	3.3	70	11.5	79	5	Normal	
12 (35 M)	134 gm. in 22 days (1st course)	Before	4.8	75	12.6	73			Fourteenth and 25th days, blood smears similar to Case 1. Color index, 0.9. Forty-eighth day, 500-cc. blood transfusion prior to second course of sulfanilamide.
		After:							
		14th	3.2		10.7	87	3	Normal	
		25th	3.0	60	7.5			Normal	
		46th	4.8	60	8.7				
13 (27 M)	82 gm. in 13 days (1st course)	Before	4.6	80	14.0	67			Thirteenth day, blood smear similar to Case 1. Color index, 0.9. No treatment for anemia.
		After:							
		13th	3.5	60	14.1	60	5	Normal	
		50th	4.7	70	10.8			Normal	
		76th	4.2	70	8.5				
14 (26 M)	126 gm. in 21 days	Before	3.8	65	9.9	72			Twenty-eighth day, blood smear similar to Case 1. Color index, 1.0. Thirty-ninth day, 500-cc. blood transfusion.
		After:							
		28th	2.9	50	10.3	62	3	Normal	
		40th	4.2	75	10.0			Normal	
16 (30 F)	94.5 gm. in 18 days	Before	4.3	80	10.5	75			Thirteenth day, blood smear similar to Case 1. Twenty-first day, volume index 1.2, color index 1.0. After 14th day, 1.02 gm. of ferrous sulfate given daily for 3 weeks.
		After:							
		13th	3.7	70			13	Normal	
		18th	3.7	82			10	Normal	
		21st	3.5	74	5.5		6		
		58th	4.5	102					
25 (37 F)	84 gm. in 14 days	Before	3.5	65	10.7		Not done	Not done	Fifteenth day, blood smear similar to Case 1. Twenty-fifth day, 500-cc. transfusion given as supportive measure for arthritis.
		After:							
		9th	3.2		12.3	67			
		15th	2.4	45					
		25th	3.4	70	13.7				
		32nd	3.5		9.0	75			
27 (44 F)	90 gm. in 24 days	Before	4.3	64	9.1	69	0.4		Twentieth day, blood smear similar to Case 1. Anemia not treated.
		After:							
		20th	2.7	65	4.8	65	6	2.5 mg. %	
		24th	2.6	65	5.6	35	0.4		
		29th	3.7	70	6.1	78			
		64th	4.3		8.3	57			

*Hemoglobin determinations cannot be read accurately during sulfanilamide therapy.

She received 7 gm. a day for 7 days. This dosage maintained a blood-sulfanilamide level of 9.4 mg. per cent. Forty-eight hours after institution of sulfanilamide therapy there was marked reduction of pain and swelling. Much of the redness and throbbing pain had disappeared. Three days after starting therapy there was 10 degrees of painless motion. One week after treatment the knee could be flexed 45 degrees and extended to 180 degrees. Ten days later 90 degrees of flexion was possible without pain. At this time a moderate degree of soft-tissue swelling persisted, particularly in the region of the quadriceps pouch. At the time of the 7-week follow-up, walking was painless, extension 180 degrees and flexion 90 degrees.

No synovial fluid was obtained on the 3rd day, and that aspirated on the 4th day was sterile. The blood complement-fixation test on the day of entry was negative and never became positive, whereas the synovial fluid obtained on the day of entry was positive. The initial sedimentation rate was 1.75 mm. per minute; 3, 5, 7, 11 and 13 days later it was 1.36, 1.36, 0.43, 0.25 and 0.18 mm. respectively. The hematologic variations noted were a reticulocytosis of 22 per cent, a macrocytic anemia and a marked leukocytosis (Table 3). The serum bilirubin remained normal. The serum carbon-dioxide combining power fell to 48.3 vol. per cent. The lowest serum chloride observed was 97 milliequivalents.

Roentgenograms taken 10 days after cessation of therapy revealed no effusion and only slight soft-tissue swelling. The previously described changes were still present but seemingly less marked. Four weeks later the flecky decalcification and a small area of destruction in the tibial condyle were still present. Four weeks later the x-ray report read: "The joint surfaces visible are well restored. Subchondral, flecky decalcification in the subchondral regions of all the bones forming the knee joint is still present. No soft-tissue swelling is demonstrable."

Cyanosis and mild vertigo were present during the period of treatment. No other toxic symptoms were noted.

Summary. An acute case of proved gonorrheal arthritis of 21 days' duration was promptly arrested by the institution of sulfanilamide therapy, as shown by marked subsidence of the joint signs and symptoms and sterilization of the synovial fluid.

Case 3. K. W., an 18-year-old, single Negress, entered the hospital with a diagnosis of acute rheumatic fever. Ten days prior to entry she had developed an acute upper-respiratory infection with associated sweating, malaise and generalized aching. One day later the right wrist and both elbows became hot, swollen and tender. There was no previous history of genitourinary or arthritic symptoms.

Physical examination was normal except for exquisitely painful and swollen right wrist and elbows, acute endocervicitis and a profuse vaginal discharge. The left elbow was so painful as to forbid motion. Gonococci were found in the synovial fluid from the left elbow and in the cervical smears. During the 8 days preceding sulfanilamide therapy analgesics and opiates were necessary to control pain. During this time the temperature fluctuated between 99.5 and 103°F. X-ray examination showed marked soft-tissue swelling of the involved joints and atrophy of the bones of both elbows.

Eight days after entry sulfanilamide therapy was begun, the patient receiving 6.6 gm. per day for 12 days. Forty-eight hours after the institution of therapy analgesics and opiates were no longer required, the motions present were painless and marked reduction of the swelling had occurred. From this time on improvement was rapid. Three days later massage and passive motions were begun. At this time the left elbow had approximately 120 degrees of motion. Nine days after cessation of treatment the joints were symptom-free and motions were normal except for the left elbow, which lacked 5 degrees of full extension. Five pelvic smears after the 1st day of treatment were negative. The blood complement-fixation test, which was doubtful on entry, never became positive. The initial sedimentation rate was 2.12 mm. per minute; 1, 3 and 4 weeks later it was 1.95, 1.84 and 1.07 mm. respectively. Sulfanilamide therapy apparently caused a marked macrocytic anemia, a reticulocytosis of 20 per cent and a leukopenia of 1800 (Table 3). Icterus, bilirubinemia and urobilinogenuria were never demonstrable.

Repeated x-ray examinations revealed no other changes than those noted. The effusion and soft-tissue swelling disappeared 3 weeks after the institution of therapy.

The patient was slightly drowsy and occasionally euphoric during the period of treatment. No other toxic symptoms were observed.

Summary. A patient with proved acute gonorrheal arthritis and endocervicitis made an excellent recovery after 12 days on large doses of sulfanilamide. At the time of discharge she had slight stiffness of the left elbow on full extension.

These 3 cases of proved acute gonorrheal arthritis with infected synovial fluids were promptly arrested following the administration of large doses of sulfanilamide. Cases 1 and 3 illustrate the desirability of instituting such therapy as early as possible if irreparable joint damage is to be prevented and normal joint function preserved. In Case 2 the response to therapy was equally as prompt as in Cases 1 and 3, as shown by the marked clinical improvement and sterilization of the infected synovial fluid. Repeated roentgenograms demonstrated that destruction of the joint was arrested and recalcification of the subchondral bone made possible. However, sufficient intra-articular changes had taken place prior to the institution of therapy to prevent restoration of normal joint function. From the results in these cases it is apparent that with large doses of sulfanilamide marked clinical improvement can occur as early as forty-eight to seventy-two hours following their institution. Corroborative laboratory evidence of this improvement is obtained from repeated synovial-fluid analyses. Such analyses reveal that the infected fluid may become sterile within forty-eight hours (Table 1). With the sterilization of the synovial fluid the cytologic abnormalities may be restored to practically normal values within seven days. The genitourinary foci seemed to respond equally as well to sulfanilamide, in that no gonococci were isolated after forty-eight hours of therapy. The blood complement-fixation test never became positive in these cases. These results suggest that if large doses of sulfanilamide are to be therapeutically effective in a given case, improvement may be expected as early as forty-

Table 4. *Clinical Results Observed in Patients with Gonorrheal Arthritis Treated with Sulfanilamide.*

Case No. (Age and Sex)	Duration of Infection		Sulfanilamide		Time in Relation to First Day of Therapy	Toxic Manifestations	Laboratory Data				Case Summary and Remarks
	Genito-urinary	Joints	Daily dose	Blood level			Sedimentation rate	Lowest plasma carbon dioxide combining power	Variations of serum chlorides	Serum bilirubin	
	days	*days*	*gm.*	*mg. %*	*day*		*mm. per min.*	*vol. %*	*milliequiv.*		
4 (36 F)	8	6	8.0 (2 days) 6.0 (18 days) 1.3 (5 days)	10.0+ 10.0+	Before After: 21st 84th	Cyanosis, anemia,* leukopenia.	1.87 0.54 0.36	50.1	101-104	Normal	Severe acute arthritis (proved) of the left ankle and small joints of the left foot, requiring morphine. Roentgenograms showed atrophy and soft-tissue swelling. Marked reduction of pain and swelling after 48 hours' therapy. Sedation and analgesics discontinued and cast removed. Uneventful recovery, 8-month follow-up. Roentgenograms showed recalcification.
5 (18 F)	9	8	7.0 (1 day) 4.0 (3 days) 6.0 (6 days)		Before After: 7th 140th	Cyanosis; 10th day exposed to sunlight; few hours later, edema and purplish discoloration of face, neck and hands.	1.78 0.57 0.35	Not done	Not done	Not done	Moderate, severe, acute arthritis (proved) of right wrist, ankle and small joints of foot, associated with petechial rash. Roentgenograms showed soft-tissue swelling. Marked subsidence of pain and swelling after 72 hours' therapy. Complete recovery in 4 weeks. Remained well during a 6-month follow-up period.
6 (27 F)	?	7	6.0 (5 days) 4.0 (6 days)		Before After: 8th 56th	Cyanosis, lassitude, nausea, methemoglobinemia, anemia.*	Not done 0.28	53.6	92-101	Normal	Severe acute arthritis (proved) of left shoulder, requiring morphine. Roentgenograms showed atrophy and effusion. Pain and swelling improved after 48 hours' therapy. Effusion disappeared. Two months later there was no pain, but 10-degree limitation in external rotation remained.
7 (40 M)	24	20	6.0 (14 days) 2.0 (11 days)	12.0+	Before After: 14th 21st	Cyanosis, anorexia, drowsiness, euphoria.	1.27 0.74 0.54	53.9	101-103	Normal	Severe acute arthritis (proved) of right wrist with x-ray evidence of joint destruction on entrance. Much less pain after 72 hours' therapy. Motions 95 per cent normal in 2 weeks. Back to work as a barber in 6 weeks. Roentgenograms showed recalcification. Two-month follow-up, 95 per cent motion.
8 (53 M)	60	14	6.0 (5 days) 4.0 (4 days) 2.6 (6 days)		Before After: 28th	Cyanosis, nausea, vertigo, leukocytosis (following therapy).	Not done	55.3	101	Normal	Painful left calcaneus and acute arthritis (proved) of left ankle. Roentgenograms showed periostitis and slight joint destruction. After 3 days much less pain. Slight residual ache in left ankle, 1-month follow-up. Three months later, symptom-free, roentgenograms normal except for residual periostitis.
9 (36 M)	14	2	7.0 (7 days) 9.3 (1 day) 7.0 (6 days)	6.5+ 11.8 11.8+	Before After: 1st 10th 14th 21st 31st	Cyanosis, anemia.*	Not done 1.51 1.00 0.88 0.62 0.33	Not done	Not done	Not done	Mild, acute arthritis (proved) of right wrist with tenosynovitis. During the first 7 days of therapy, no improvement in arthritis or genitourinary symptoms. Forty-eight hours after increasing dose of sulfanilamide, joint pain decreased and smears became negative for gonococci. One hundred per cent recovery of joint function, 12-week follow-up period.
10 (42 M)	30	18	6.0 (3 days) 7.3 (1 day) 6.0 (39 days)	5.0+ 11.0+ 9.0+	Before After: 10th 16th 40th	Cyanosis, anemia.*	1.32 0.68 0.53 0.68	50.8	98-107	Normal	Severe, acute arthritis (proved) of left 2nd, 3rd and 4th metatarsophalangeal and left sacroiliac joints. Slow improvement of arthritis during first 72 hours of therapy. This improvement was greatly accelerated when the dose of sulfanilamide was increased. Roentgenograms negative except for decalcification of left sacroiliac joint. One hundred per cent recovery, 8-week follow-up.
11 (32 M)	14	7	6.0 (2 days) 4.8 (1 day) 3.0 (5 days) 6.0 (17 days)		Before After: 5th 12th 26th 35th	Urticarial rash and edema of face, 22nd day; fever, anemia,* methemoglobinemia.	Not done 1.32 1.22 0.57 0.38	55.3	96-100	Normal	Severe, acute arthritis (proved), right sacroiliac, left knee and costosternal joints. Bilateral conjunctivitis (proved). Marked improvement of arthritis and conjunctivitis during the first 48 to 72 hours of therapy. One hundred per cent recovery, 12 days after stopping therapy. Symptom-free, 6-month follow-up.

12 (35 M)	10	5	8.0 (1 day) 6.0 (21 days)	 6.0+	Before After: 15th 29th 35th	Cyanosis, anemia.*	1.50 1.30 0.97 1.35	55.5	98-105	Normal	Severe, acute arthritis (proved) of left knee, ankle, 2nd and 3rd metacarpophalangeal joints. Small doses of sulfanilamide prior to entry had no effect on arthritis, conjunctivitis or genitourinary symptoms. Smears negative 48 hours after giving sulfanilamide in large doses. Arthritis unaffected. Second course of sulfanilamide (larger doses) followed by marked improvement of arthritis in 72 hours. No residual joint symptoms or signs.
			(second course) 2.0 (6 days) 4.0 (6 days) 6.0 (6 days) 8.0 (6 days)	 3.1 5.6 10.4+ 15.0+	 66th 76th 78th 85th 140th	Cyanosis, nausea, methemoglobinemia.	 0.94 0.74 0.51 0.40 0.10	41.0	Not done	Not done	
13 (27 M)	74	5	8.0 (2 days) 6.0 (11 days)	6.6+ 6.5+	Before After: 8th 22nd	Cyanosis, anemia.*	1.90 1.73 1.51	55.5	97-106	Normal	Severe, acute arthritis (proved) of left knee, right foot and temporomandibular joint. Bilateral conjunctivitis, acute urethritis and prostatitis; 15 gr. sulfanilamide each day for 6 days, 3 weeks prior to entry, without effect on the above complaints. Seventy-two hours after large doses, urethritis, prostatitis and conjunctivitis disappeared. Arthritis unchanged. Second course of therapy resulted in marked improvement of arthritis within 72 hours, once the patient received 8 gm. daily. Uneventful recovery without joint residual.
			(second course) 6.0 (1 day) 8.0 (13 days)	 6.0+ 10.0+	 49th 63rd 112th	Cyanosis, nausea.	 1.97 1.11 0.86	59.5	Normal	Normal	
14 (26 M)	150	134	6.0 (7 days) 6.0 (14 days)	11.7— 17.4	Before After: 14th 21st 35th 77th 119th	Cyanosis, anemia.*	1.61 1.43 1.63 1.21 1.09 0.58	50.7	105-109	Normal	Severe, chronic arthritis (proved) of fingers, wrists, elbows, shoulders, knees, ankles and feet and marked keratodermia blennorrhagicum of 4½ months' duration. Roentgenograms revealed soft-tissue swelling, marked bone atrophy and flecky decalcification of the involved joints. Small doses of sulfanilamide prior to onset of arthritis without effect on urethritis. Sulfanilamide in large doses resulted in slow, steady improvement of arthritis and keratodermia. No effect on prostatitis. Ten days of Neosilvol instillations given. Four months later, normal skin and nails, residual deformity of second midphalangeal joints; other joints normal. Smears and cultures after three prostatic massages were all negative for gonococci. Back at work as a carpenter.
15 (26 F)	?	7	4.0 (29 days)		Before After: 21st 140th	Cyanosis	1.53 0.23 0.18	54.7	104-107	Normal	Severe, acute arthritis (probable) of wrists, knees, left metacarpophalangeal and metatarsophalangeal joints. Tenosynovitis, left wrist. Roentgenograms showed soft-tissue swelling. Forty-eight hours after starting sulfanilamide, sedatives discontinued and swelling had subsided. Two and one-half weeks later, walking, symptom-free. Three-month follow-up, 100 per cent recovery.
16 (30 F)	42	21	4.0 (12 days) 3.0 (14 days)		Before After: 14th 63rd	Cyanosis, vertigo, anorexia, anemia,* methemoglobinemia.	1.79 0.43 0.37	52.7	102	Normal	Subsiding. acute arthritis (probable) of right wrist with roentgenographic evidence of joint destruction and narrowing. Four days after therapy, pain less and cock-up splint removed. Four months later, 5 per cent motion in right wrist.
17 (26 M)	90	75	10.7 (1 day) 8.0 (16 days) 6.0 (12 days) 8.0 (7 days)	9.0+ 6.2+ 6.2+ 10.5+	Before After: 7th 14th 35th 42nd	Cyanosis	0.61 0.38 0.68 0.30 0.39	42.0	101-109	Normal	Moderate, chronic arthritis (probable) of left calcaneus, right ankle, knees, right sacroiliac. Roentgenograms showed flecky bone atrophy. After starting of therapy joint pain and effusion of the right knee gradually subsided during a 2-week period. Four-month follow-up, 100 per cent recovery.
18 (35 F)	60	54	6.0 (10 days)		Before After: 120th	Cyanosis; urticaria and edema of face on 10th day.	0.90 0.32	Not done	Not done	Not done	Subacute, subsiding arthritis (probable) of right shoulder, elbow, wrist and hand. Right hand swollen with muscle atrophy. Roentgenograms of right elbow joint showed atrophy, narrowing and new bone formation. Very gradual improvement of pain and swelling during 10 days of therapy. Eleven-month follow-up, 90 per cent recovery of normal joint function.

*See Table 3 for detailed data concerning anemia.

eight to seventy-two hours after institution of treatment.

Proved Gonorrheal Arthritis with Synovial Fluids Containing No Demonstrable Gonococci

Six (Cases 4, 5, 6, 7, 8, and 11) of the remaining 11 patients with proved gonorrheal arthritis obtained marked relief of their joint symptoms two to three days after the institution of sulfanilamide therapy (Table 4). Of these 6 patients, 4 (Cases 4, 5, 8 and 11) made uneventful recoveries with complete restoration of joint function. Two patients (Cases 6 and 7) failed to regain normal joint function. Their joints were 90 to 95 per cent normal at the time of the last follow-up. In these 2 cases there was roentgenologic evidence of joint destruction prior to treatment.

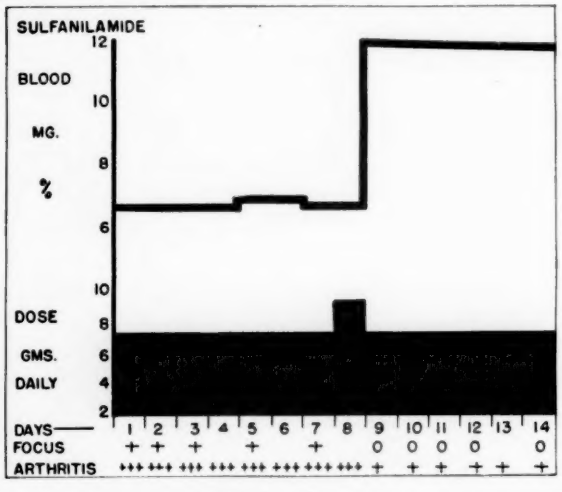

Chart 1. *Case 9.*

This chart shows that the gonococcal prostatitis and arthritis failed to respond when the blood-sulfanilamide level was kept at 6.4 mg. per cent. Twenty-four hours after reaching a level of 11.8 mg. per cent, the joint pain diminished and gonococci disappeared from the prostatic smears and cultures.

Two patients (Cases 9 and 10) in this group with arthritis of short duration and no roentgenologic evidence of joint destruction failed to show obvious improvement in their joint symptoms until the sulfanilamide dosage had been increased sufficiently to raise the blood-level above 10 mg. per cent. They both regained normal joint function. In Case 9 the genitourinary focus did not become negative until the blood sulfanilamide reached 11 mg. per cent (Chart 1).

Two other patients (Cases 12 and 13) with arthritis of four and seven days' duration and without roentgenologic evidence of joint destruction were first treated with large doses for thirteen and twenty-two days respectively. In neither case was the improvement in the arthritis any more rapid than might be expected with good conservative treatment and bed rest. The blood-sulfanilamide level never rose above 6.8 mg. per cent in either patient. Although the arthritis was seemingly uninfluenced by the drug, gonococci could not be isolated from the genitourinary foci after the second day. The fixation tests became negative forty-three and forty-four days respectively after cessation of therapy. From Table 5 it is seen that the cytologic abnormalities in the synovial fluid were uninfluenced by the drug, corroborating the clinical impression that no improvement in the arthritis had occurred. These 2 patients had received small doses (10 to 15 gr. three or four times a day) of sulfanilamide prior to entry, without benefit. The drug was readministered in both these cases (Table 4, Cases 12 and 13) in order that we might note the effect of therapy with a blood level of 10 mg. per cent or higher. Seventy-two hours after the blood-sulfanilamide level had reached 10 mg. per cent the joint pains had subsided. One week later the knee effusions had completely disappeared.

One patient (Case 14) entered the hospital during the fifth month of his arthritis. He had an associated keratodermia blennorrhagicum, with the characteristic skin and nail lesions. His improvement following sulfanilamide administration (large doses for 7 days on one occasion and 14 days on another) was very slow but progressive. The skin and nail lesions seemingly cleared more rapidly than they do in untreated cases. Despite the fact that he received sufficient sulfanilamide to maintain a blood-sulfanilamide level from 11.7 to 17.4 mg. per cent, gonococci were still present in the prostatic smears after the two courses of therapy.

This patient had also received small doses of sulfanilamide prior to the onset of his arthritis. At the time of discharge five weeks after the second course of sulfanilamide therapy, the skin and nails were normal but there was still some residual morning aching and stiffness. The deformity of the left first metacarpophalangeal and the right first midphalangeal joints persisted. Two months later the patient returned to his work as a carpenter and was normal except for the last-mentioned residual joint deformities. Because of failure to cure the genitourinary focus, he was given 10 per cent Neosilvol urethral instillations three times a day for ten successive days prior to discharge. During the follow-up period he received prostatic massages two or three times a week. Three months following discharge gonococci were no longer demonstrable in the prostatic smears. Three subsequent prostatic smears and cultures obtained after this were likewise negative for gonococci.

Thus it will be seen that in this group the results were equally as satisfactory in Cases 4, 5, 6, 7, 8 and 11 as they were in the patients with infected synovial fluids. The results in Cases 9, 10, 11 and 12 suggest that blood-sulfanilamide levels of 10 mg. per cent or higher are at times necessary to bring about clinical cures. It is interesting that the patients (Cases 12, 13 and 14) who did not respond so favorably as the others in this group had received small doses of the drug —and during the day only—prior to hospital entry. This might be interpreted to mean that sulfanilamide administered in doses too small to effect a cure may increase the resistance of the organism. The clinical results observed in these last 3 cases suggest the possibility that the organisms in the joint and the genitourinary focus were not equally susceptible to the drug. However, we have no proof for such statements.

Table 5. *Synovial-Fluid Findings in Two Cases of Gonorrheal Arthritis Which Failed to Respond to the First Course of Sulfanilamide Therapy.*

Case No. (Age and Sex)	Daily Dose of Sulfanilamide	Time in Relation to First Day of Therapy	Synovial Fluid Findings*				
			Amount	Leukocytes	Polymorphonuclear Leukocytes	Culture	Gonococcal Complement-Fixation Test
	gm.	*day*	*cc.*	*per cu. mm.*	%		
12 (35 M)	8.0 (1st day)	Before	85	16,000	89	Negative	Positive
	6.0 (21 days)	After:					
		2nd	20	68,000	95	Negative	Positive
		7th	60	29,100	86	Negative	
		14th	40	8,700	88	Negative	Positive
		21st	10	11,200	78	Negative	
		27th	10	12,200	2	Negative	
		35th	10	18,900	68	Negative	Positive
13 (27 M)	8.0 (1st 2 days)	Before	60	23,000	98	Negative	Negative
	6.0 (11 days)	After:					
		2nd	46	49,000	94	Negative	Negative
		7th	40	17,900	63	Negative	
		14th	40	11,300	58	Negative	Positive
		21st	18	4,800	52	Negative	Negative
		36th	40	10,200	78	Negative	

*Synovial-fluid sugars in both instances were normal throughout the period of observation.

The results obtained in these 11 cases show that proved gonorrheal arthritis without demonstrable gonococci in the synovial fluids, if treated with large doses of sulfanilamide, may respond equally as well and as promptly as do cases having infected synovial fluids. They also demonstrate the necessity of adequate treatment being instituted early if the largest potential percentage of cures without residual joint changes is to be obtained.

Probable Gonorrheal Arthritis

Two of the 4 patients with probable gonorrheal arthritis (Cases 15 and 16) responded as promptly to sulfanilamide therapy as did any one of the patients in the two previous groups. In Case 15 there was complete recovery. Case 16 showed roentgenologic evidence of joint destruction prior to treatment and only 5 per cent normal motion was regained. In the 2 remaining patients (Cases 17 and 18) with probable gonorrheal arthritis immediate improvement forty-eight to seventy-two hours after the institution of therapy was not observed. In Case 17, although the arthritis had been present for seventy-five days before receiving the drug, the roentgenograms revealed no evidence of joint destruction. This patient made a complete recovery except for slight residual aching. In Case 18 the patient showed evidence of narrowing and destruction of the left elbow joint at the time of entrance into the hospital, fifty-four days after onset of her disease. She improved gradually. At the time of the last follow-up the left elbow joint had 90 per cent of normal motion. At the onset of her arthritis this patient had received 5 gr. of sulfanilamide four times a day for twenty-one days.

The results in this group again suggest the importance of early treatment with large doses in order to obtain the highest percentage of clinical cures.

Rheumatoid Arthritis

In an attempt to establish that the clinical cures observed in this group of patients with gonorrheal arthritis represented a specific effect of sulfanilamide therapy on the gonococcus, it was deemed necessary to obtain similar data from cases with some other type of arthritis. Patients with rheumatoid arthritis were chosen because this disease is one of unknown etiology and has many features suggesting an infectious origin. It was thought that the results obtained in this group would also enable us to determine whether or not rheumatoid arthritis is due to an infectious agent

which is similarly affected when exposed to large doses of sulfanilamide.

A total of 10 patients with rheumatoid arthritis were treated. Nine of them received large doses of sulfanilamide for periods varying from eight to twenty-seven days (Table 6). In Case 19 the patient became so apprehensive because of mild gastric symptoms and vertigo that the dose was reduced on the third and fourth days and was discontinued four days later. Except in Case 20 there occurred no improvement in joint symptoms and no appreciable drop in sedimentation rates during the time sulfanilamide was given or during the subsequent follow-up periods. In fact, 2 of the patients (Cases 21 and 22) developed joint effusions during the period of therapy. In Case 20 the patient, who had typical mild rheumatoid arthritis of seven and a half months' duration, experienced almost complete relief subsequent to the development of a continuous fever (102 to 103°F. for eight days). The fever disappeared promptly following the discontinuance of the drug. In this case the sedimentation rate returned to normal ten days after treatment. It was still normal nine weeks later. At this time the patient complained of joint symptoms, which required acetylsalicylic acid for control. Judging from our past experience with fever therapy in patients with rheumatoid arthritis,[35] it seems fair to ascribe the improvement noted in this particular case to the eight days of continuous fever caused by the drug. Mild rheumatoid arthritis of short duration is the type which responds most favorably to fever therapy.

In Case 22 the gonorrheal urethritis and prostatitis of six months' duration were clinically cured after the third day of therapy, but the arthritis of four years' duration was unaffected. In Case 21, with a chronic prostatitis of ten years' duration and a positive complement-fixation test, the patient noted no improvement in his arthritis (eight years' duration) during or following sulfanilamide therapy. The prostatitis improved and the complement-fixation test became negative. Case 24, with mild rheumatoid arthritis of four months' duration, showed a chronic prostatitis (seventeen years' duration) and a positive complement-fixation test. Sulfanilamide therapy resulted in marked improvement in the prostatitis and the complement-fixation test became negative. The arthritis, however, was uninfluenced.

From the clinical results obtained in these 10 cases of rheumatoid arthritis, it seems fair to conclude that sulfanilamide therapy does not exert any specific effect on the agent causing rheumatoid arthritis, nor does it influence the course of the disease. Failure to affect the arthritis in 3 of these patients, despite the fact that the gonococcal foci improved, is further evidence that sulfanilamide has a specific effect on the gonococcus and none on the agent responsible for rheumatoid arthritis.

Effect on the Sedimentation Rate

The sedimentation rate was tested at frequent intervals in order to determine whether it fell as the gonorrheal arthritis improved. From Table 4 and Chart 2 it will be seen that such a relation

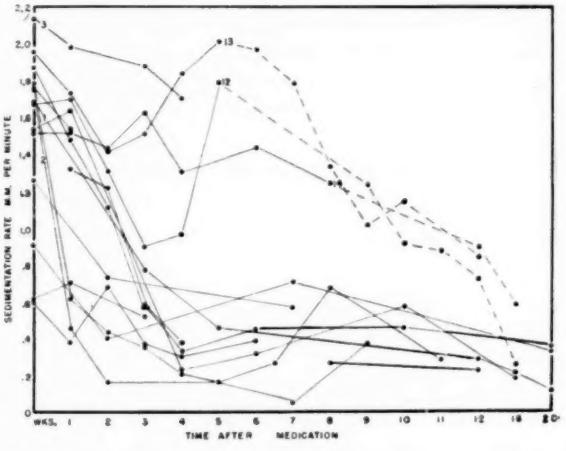

Chart 2. *Corrected Sedimentation Rates in Cases of Gonorrheal Arthritis.*

Here one notes that there occurred a rapid decrease in the corrected sedimentation rates of the bloods of most of the patients with gonorrheal arthritis following the institution of sulfanilamide therapy. Cases 1, 2 and 3 had infected synovial fluids. Cases 12, 13 and 14 did not respond to the first course of sulfanilamide therapy (solid line) but did respond when it was administered a second time (broken line). The normal corrected sedimentation rate varies from 0.08 to 0.35 mm. per minute.

was found with great regularity. It should be noted that the most rapid decrease in sedimentation rate took place in the patients showing striking improvement and that in the cases which improved slowly a correspondingly slow return of the sedimentation rate to normal was observed. The sedimentation rates remained fairly constant in 3 patients (Cases 12, 13 and 14) during the time the arthritis remained stationary or improved slowly. In Cases 2, 5, 6, 11, 15, 16 and 17 it returned to normal in four weeks. Such rapid falls in sedimentation rates are rarely observed in gonorrheal arthritis with other forms of treatment except in mild cases. With other forms of therapy it frequently remains elevated for three to twelve months. From Table 6 and Chart 3 one notes that the sedimentation rates remained unchanged or were only slightly altered in the 10 cases of rheuma-

Table 6. *Results Observed in Patients with Rheumatoid Arthritis During and Following Sulfanilamide Therapy.*

Table 6. *Results Observed in Patients with Rheumatoid Arthritis During and Following Sulfanilamide Therapy.*

Case No. (Age and Sex)	Duration of Joint Symptoms	Sulfanilamide: Daily Dose	Sulfanilamide: Blood Level	Time in Relation to First Day of Therapy	Toxic Manifestations	Laboratory Data: Sedimentation Rate	Laboratory Data: Lowest Plasma Carbon Dioxide Combining Power	Laboratory Data: Serum Chlorides	Case Summary and Remarks
	yr.	*gm.*	*mg. %*	*day*		*mm. per min.*	*vol. %*	*milliequiv.*	
19 (48 M)	27	8 (3 days) 6 (1 day) 4 (5 days)		Before After: 90th	Cyanosis, vertigo, nausea.	Not done 1.23	Not done	Not done	Mild atypical progressive rheumatoid arthritis and chronic nonspecific prostatitis. No improvement of joint symptoms during therapy. Arthritis unchanged at the end of a 3-month follow-up period.
20 (40 M)	2/3	6 (11 days)		Before After: 7th 14th 21st 57th	Cyanosis, fever, euphoria.	0.58 0.88 0.66 0.18 0.18	Not done	Not done	Mild typical rheumatoid arthritis (acute onset). Symmetrical joint involvement. During the first 3 days of therapy, joint pain increased. Developed sustained temperature (102-103°F.) on fourth day, which continued until drug was omitted. Joint pain, swelling and stiffness improved. Sixteen weeks later, improvement maintained except for minimal stiffness and aching.
21 (32 M)	8	6 (12 days) 2 (12 days)	13.0+ 5.0+	Before After: 14th 21st 30th 56th 84th	Cyanosis	1.62 1.67 1.34 1.35 1.42 1.26	55.3	100-102	Moderately severe progressive rheumatoid arthritis (typical). Spondylitis with symmetrical joint involvement. No improvement with sulfanilamide therapy. Effusion of the left knee developed during the 3rd week of therapy. Arthritis unchanged during 6-month follow-up period.
22 (24 M)	4	6 (14 days) 2 (14 days)	8.0+ 5.0+	Before After: 19th 21st 30th 44th	Cyanosis, vertigo.	1.43 1.41 1.62 1.28 1.44	52.5	99-102	Mild slowly progressive rheumatoid arthritis (typical). Six months prior to entry contracted acute gonorrhea. No improvement of joint symptoms during sulfanilamide therapy. Urethral discharge disappeared 2nd day after therapy started. Effusion of right knee developed during the 3rd week of therapy. A 20-week follow-up period showed no change in joint symptoms.
23 (45 M)	5	6 (14 days) 2 (14 days)	12.0+	Before After: 14th 21st 42nd 63rd 77th 82nd	Cyanosis	0.70 0.96 0.37 0.63 0.59 0.55 0.52	43.8	99-109	Mild progressive rheumatoid arthritis (atypical) with knee effusion of 4 months' duration. Nonspecific prostatitis. Renal stones. Slight improvement during therapy. A 5½-month follow-up period showed condition unchanged. Knee effusion and painful shoulders persisted.
24 (34 M)	1/3	6 (15 days)			Cyanosis	Not done	58.5	101	Mild typical rheumatoid arthritis (acute onset). No improvement during sulfanilamide therapy. Joint symptoms unchanged during 16-week follow-up period.
25 (37 F)	6	6 (14 days)	5.0+	Before After: 7th 14th 21st 30th 42nd	Cyanosis, anemia.	1.41 0.84 0.58 0.80 0.92 0.93	Not done	Not done	Moderately severe progressive rheumatoid arthritis (typical) with knee effusions for 4 years. No improvement during therapy and unchanged 4 weeks after cessation of sulfanilamide.
26 (20 M)	4	6 (27 days)	6.4+	Before After: 7th 19th 28th 40th 100th	Cyanosis, slight anemia.	0.75 1.04 0.78 0.93 1.08 0.74	Not done	Not done	Moderately severe progressive rheumatoid arthritis (typical) with associated spondylitis. No improvement during or following therapy. Followed 1 month.
30 (31 M)	9	15 (1 day) 8 (8 days)	12.0+	Before After: 14th	Cyanosis, fever, anorexia, nausea, rash.	0.78 0.71	52.3	100-104	Moderately severe, slowly progressive rheumatoid arthritis (typical). Symmetrical joint involvement. Knee effusions of over 4 years' duration. Drug omitted after nine days because of appearance of a diffuse maculopapular rash. No improvement in arthritis during or following therapy.
31 (57 M)	5/6	12 (1 day) 7 (1 day) 6 (7 days)	10.0+	Before After: 10th	Cyanosis, anorexia, nausea, fever, euphoria.	0.21 0.18	45.0	99-101	Very mild, slowly progressive rheumatoid arthritis (typical). Symmetrical involvement of shoulders, wrists and fingers. No improvement during therapy despite continuous temperature of 102-103°F. No change noted during follow-up.

toid arthritis except for the previously mentioned Case 22.

These data suggest that a rapid fall in the sedimentation rate in gonorrheal arthritis is indicative of a satisfactory clinical response to the dose of sulfanilamide being administered. If the sedimentation rate remains unchanged, this may indicate inadequate dosage, a resistant gonococcal strain or an incorrect diagnosis.

Effect on the Genitourinary Focus

Gonococci were isolated from the genitourinary tract in 13 of the 14 cases of proved gonorrheal arthritis (Table 2). In 12 of these cases there was marked improvement in the genitourinary

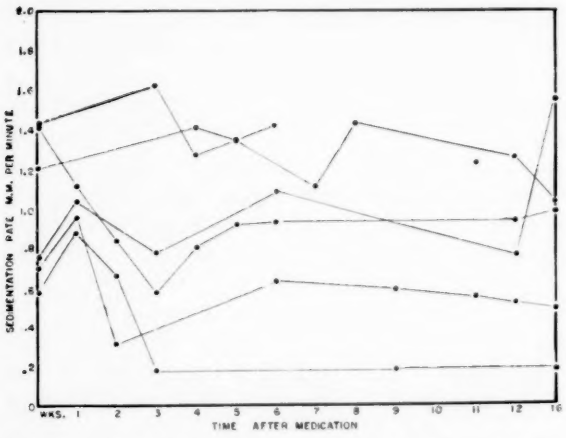

Chart 3. *Corrected Sedimentation Rates in Cases of Rheumatoid Arthritis.*

From this chart one notes that the corrected sedimentation rates of the bloods of patients with rheumatoid arthritis are not altered following the administration of sulfanilamide. The one case in which the sedimentation rate did return to normal (Case 20) developed fever on the fourth day of therapy. It continued between 102 and 103°F. during the subsequent eight days.

symptoms and disappearance of the gonococcus after the third day of therapy. Subsequent examinations three to forty-eight weeks after cessation of therapy revealed no clinical or laboratory evidence suggesting a recurrence of the genitourinary infection. In Case 9 the organisms did not disappear from the prostatic secretions until the blood-sulfanilamide level had been raised from 6.5 to 11.5 mg. per cent. Gonococci were demonstrable in the prostatic secretions from Case 14 after two periods of large doses of sulfanilamide of seven and fourteen days respectively, during which time the blood-sulfanilamide level varied between 11.7 and 17.4 mg. per cent. The genitourinary focus subsequently became negative (Tables 2 and 4). Whether the previous sulfanilamide therapy played any part in this cure we are unable to say.

Three additional cases were studied. In 2 the patients had uncomplicated gonorrhea. In 1 there was a complicating ischial bursitis. The case histories are presented in brief because of the ensuing complications.

Case 27. H. R., a 44-year-old, married woman, entered the hospital because of proved gonorrheal endocervicitis of 2 months' duration. The temperature was normal prior to treatment.

Beginning 1 day after entry the patient received 1.33 gm. of sulfanilamide every 4 hours for 2 days, then 0.66 gm. every 4 hours for 12 days, and finally 0.44 gm. every 4 hours for 10 days. Four hours after giving the second 1.33-gm. dose the blood-sulfanilamide level was 12.6 mg. per cent. This level was maintained until the dose was reduced to 0.66 gm. every 4 hours. On this dosage it varied between 4.1 and 7.4 mg. per cent.

Three sets of pelvic smears obtained after the 4th day of therapy were negative for gonococci. There was no clinical evidence of endocervicitis after the 10th day. The gonococcal complement-fixation test never became positive. The carbon-dioxide combining power fell to 45.6 vol. per cent. The serum chlorides varied between 97 and 109 milliequivalents. The serum bilirubin was 2.5 mg. per cent on the 3rd day of treatment. The hematologic changes observed are presented in Table 3.

Cyanosis was present from the 1st day on. During the first 2 days the patient had severe "seasickness," frontal headache and diarrhea. From the 5th to the 16th day of therapy the temperature varied from 101 to 103°F. (Chart 5).

Summary. A patient with proved acute gonorrheal endocervicitis made a complete recovery after 24 days of sulfanilamide therapy. During a 4-week follow-up period she remained well, all clinical examinations and laboratory tests being normal.

Case 28. J. McL., a 21-year-old, single man, entered the hospital because of a proved acute gonorrheal urethritis of 2 days' duration. The temperature was normal during the entire period of observation.

Beginning 1 day after entry the patient received 1.33 gm. of sulfanilamide every 4 hours for 14 days. Forty-eight hours after institution of therapy the urethral discharge disappeared completely. Three prostatic smears obtained after the 2nd day were negative for gonococci. The complement-fixation test never became positive. No significant hematologic variations occurred. The carbon-dioxide combining power fell to 44.6 vol. per cent. The lowest serum chloride was 101 milliequivalents. The serum bilirubin remained unchanged.

Cyanosis was present throughout treatment. On the 14th day the patient developed an acute pharyngitis, fever and a palpable spleen. Twenty-four hours later an enanthem and a faint morbilliform rash appeared. It disappeared 12 hours after discontinuance of the drug. No other toxic symptoms were noted.

Summary. A patient with acute gonorrheal urethritis made a complete recovery after 14 days of sulfanilamide therapy. During a 2-month follow-up period he has remained cured.

Case 29. G. M., a 29-year-old single man, contracted gonorrhea 42 days before entry. Seven days later he developed an ischial bursitis. He received 6 gm. of sulfanil-

amide per day, resulting in a blood-sulfanilamide level of 9.5 mg. per cent. Two days after institution of therapy the urethral discharge ceased and there was marked reduction in the bursal pain and swelling. No gonococci were demonstrable in three prostatic smears obtained after the 3rd day of therapy. The patient was completely symptom-free in 2 weeks.

Summary. A patient with proved gonorrheal prostatitis and an associated ischial bursitis made a complete recovery after 13 days of sulfanilamide treatment.

Thus it will be seen (Table 2) that in 17 of the 18 cases having a proved genitourinary focus no gonococci were isolated after the third day of treatment. These cases remained clinically cured during the three- to forty-eight-week follow-up periods. The 1 failure (Case 14) has been discussed. In another study undertaken to determine what dose of sulfanilamide will cure the greatest number of patients with gonococcal infections in the shortest period of time, we have encountered 2 cases of acute urethritis which did not respond to sulfanilamide. These patients received the drug for fifty-nine and sixty-nine days respectively. During seven days of this therapy the blood-sulfanilamide level was maintained at between 35 and 40 mg. per cent. Until the mode of action of sulfanilamide is known, it is impossible to state whether such failures represent special properties of certain gonococcal strains or failure of response in the host. The results in certain cases suggest that insufficient doses of sulfanilamide may interfere with the subsequent effect of large doses. This important point can be determined only by further study.

Effect on Gonococcal Complement-Fixation Test

The gonococcal complement-fixation tests on the blood serums from the 3 patients having proved gonorrheal arthritis with infected synovial fluids never became positive. In Case 2 the synovial-fluid complement-fixation test was positive. The serums from 11 cases of proved gonorrheal arthritis without infected synovial fluids had positive tests. In 6 of these patients the tests became negative in eighteen weeks (Case 4), ten weeks (Case 5), fourteen weeks (Case 6), five weeks (Case 8) and seven weeks (Cases 12 and 13) after the institution of sulfanilamide therapy. In only 1 (Case 18) of the 4 cases of probable gonorrheal arthritis did the test become negative during the time they were followed. In Case 22, with proved gonorrheal prostatitis and urethritis and rheumatoid arthritis, the test remained positive. It became negative within ten and seven weeks respectively in the 2 patients (Cases 21 and 24) with rheumatoid arthritis and probable gonorrheal prostatitis.

Failure to develop positive complement-fixation tests in Cases 1, 2 and 3 suggests that the patients were cured before sufficient antigen had been absorbed.

It is further seen that the serum complement-fixation test for the gonococcus became negative in 9 of the 18 patients having proved (12 cases) or probable (6 cases) gonococcal infections. The fact that the test became negative in such a large percentage of the cases in so short a period of time is further evidence that clinical cures were obtained. Following fever therapy the complement-fixation tests do not become negative in such a large percentage of the cases. They rarely become negative in less than three months' time, and frequently remain positive for as long as six or eighteen months.[73]

Toxic Manifestations Observed During Sulfanilamide Therapy

During sulfanilamide administration many toxic symptoms appeared. The commonest complaints were vertigo, drowsiness, headache, euphoria, irritability, weakness, nausea, anorexia and at times slight mental confusion. Many patients described their discomfort as being similar to seasickness. Obvious dyspnea was usually present. In no case were these symptoms indicative of serious complications.

Cyanosis. A varying degree of cyanosis is observed in all patients receiving large doses of sulfanilamide. It is apparent within the first twenty-four hours after the drug is instituted, and disappears rapidly after it is discontinued. In view of the fact that it has been shown that the oxygen capacity of the blood is not diminished, the cyanosis cannot be considered a contraindication to the continuance of therapy.[37] Hartmann et al.[38, 39] report that the cyanosis disappears if 1.5 mg. of a 10 per cent aqueous solution of methylene blue per kilogram of body weight is given intravenously. They further report that it can be prevented if methylene blue is administered by mouth with each dose of sulfanilamide.

This finding and the demonstration of methemoglobin values as high as 13 mg. per cent in patients receiving sulfanilamide have led Hartmann and his associates to conclude that the cyanosis is due to methemoglobin. Other workers[3, 40–44] have reported that the cyanosis is due to either sulfhemoglobin or methemoglobin in the circulating erythrocytes. Posner and his coworkers[45] suggest that such methemoglobin is unstable, thus accounting for the inability to demonstrate regularly its presence in the blood of "sulfanilamide-cyanotic" patients. Marshall and Walzl[37] were able to demonstrate its presence in

the blood of only 1 of 3 patients whose hemoglobin as measured by oxygen capacity corresponded with the theoretical value obtained from the total iron content of the blood. They therefore concluded that methemoglobin plays an insignificant role in the production of the cyanosis. They and others[46] suggest that the erythrocytes, which appear brown even after the blood has been thoroughly aerated, are stained by a pigment formed from sulfanilamide. More recently the same suggestion has been made by Ottenberg and Fox[47] on the basis of experiments in vitro. They demonstrated the development of a violet color when clear solutions of sulfanilamide (10 to 20 mg. per cent) were irradiated. When such a solution was added to plasma, the violet color disappeared and the erythrocytes became brown as they do in patients receiving sulfanilamide. These authors venture the supposition that the same violet pigment is made in vivo during the metabolism of sulfanilamide and that it accounts for the cyanosis. There is, however, no actual evidence for such a theory. Further work is necessary before the exact cause of the cyanosis can be stated.

"Acidosis." Since the original report of Southworth,[34] most writers have noted a reduction in the plasma carbon-dioxide combining power. We have observed similar changes. Often the values obtained were within the normal range, but in every case the premedication values were higher than those obtained during therapy. The lowest serum carbon-dioxide combining power observed was 41 vol. per cent (Case 12). The average reduction observed was 10 vol. per cent. This reduction of the carbon-dioxide combining power occurred even though the patients received amounts of sodium bicarbonate equal to the sulfanilamide dosage.

This lone blood chemical alteration has been interpreted as signifying the existence of acidosis. That such might not be the case was first suggested by Hartmann and his co-workers.[38, 39] They observed that the hyperventilation resulting from moderately large doses of sulfanilamide simulated the dyspnea of acidosis, yet only moderate reductions (15 to 20 vol. per cent) of carbon-dioxide content of the blood were demonstrable. Further studies revealed that coincident with the fall in the carbon-dioxide content of the serum there occurred a rise in serum pH and the production of an alkaline urine. These findings led the investigators to conclude that the changes in the acid-base equilibrium represented a carbon-dioxide-deficit type of alkalosis secondary to primary hyperventilation, and not acidosis. They have suggested, that the routine administration of alkali in conjunction with sulfanilamide is not indicated.

Direct determinations made in this laboratory are in agreement with the theory proposed by Hartmann and his associates; namely, that hyperventilation occurs after the administration of large doses of sulfanilamide.[48] Whether or not primary hyperventilation is the sole cause for the observed changes in acid-base equilibrium is a question requiring further study. Detailed studies of the electrolyte metabolism reveal that the first effects noted following the administration of sulfanilamide are a striking increase in urinary total base excretion (chiefly sodium), a marked reduction in ammonia output and a strongly alkaline urine (pH 7.4 to 7.8). The serum-sodium concentration falls 5 or 6 milliequivalents. There occurs a corresponding lowering of the serum carbon-dioxide content. Within a few days the sodium and ammonia excretion and the urinary pH return to pre-treatment values despite continuance of the drug. The lower serum-sodium concentrations, however, persist so long as the drug is given (twenty-eight days in one experiment). When it is discontinued the reverse phenomena are observed: sodium is retained, the serum-sodium concentration returns to its normal level, the excretion of ammonia is increased and the urine becomes acid. The excretion of potassium follows a course similar to that of sodium but of considerably less magnitude.[48] These and other observations on the electrolyte metabolism will be published in detail at a later date.

Anemia. Severe hemolytic anemias, such as have been reported as occurring on the third to fifth day of treatment,[2, 3, 49–51] were not observed in any of these patients. Elevation of the serum bilirubin occurred in Case 27 on the fourteenth day of therapy; it was normal on the twentieth day. No other cases of bilirubinemia were observed. Jaundice was never noted in Case 27 or in any of the other cases. Urobilinuria was never found. Thirteen of the 27 patients developed a moderate to marked anemia (Table 3 and Chart 4). In these patients there occurred a progressive fall in the erythrocyte counts, the lowest levels being reached at the time therapy was discontinued, except in Case 2, where the lowest count was observed seven days later. In most cases the severe anemias were characterized by color and volume indices over 1.0. The stained blood films showed the red cells to be well filled with hemoglobin, the predominant cells being macrocytes, although microcytes and immature erythrocytes were seen. Reticulocyte responses varying from 5 to 22 per cent were observed in 9

patients. The counts were highest when the erythrocyte levels were lowest. Following the reticulocytosis there occurred a spontaneous rise in the erythrocyte counts to the pre-treatment level. The patients receiving treatment other than transfusions for their anemia responded no more rapidly than did those who were untreated. As can be seen from Table 3, the severity of the anemia was not necessarily related to the amount of sulfanilamide administered or to the length of time it was given. In some cases a leukocytosis developed subsequent to the administration of the drug. The total leukocyte count in Case 2 reached 28,000.

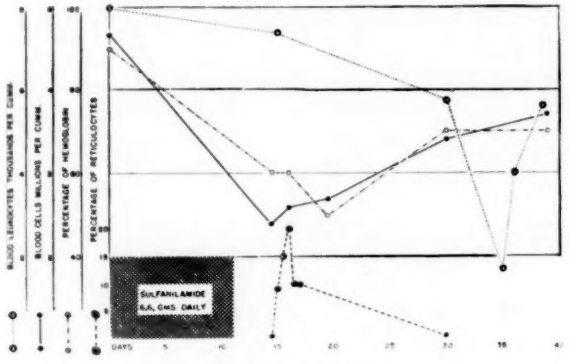

Chart 4. *Case 3.*

This chart represents the hematologic changes encountered following the administration of sulfanilamide. It will be noted that spontaneous reticulocytosis took place after the maximal drop in the erythrocyte count had occurred. The leukopenia was observed twenty-two days after the cessation of sulfanilamide therapy. From Table 3 one notes that this type of sub-clinical hemolytic anemia was encountered in 13 of the 28 patients treated with sulfanilamide.

The hematologic changes observed in these patients suggest that sulfanilamide therapy may cause a progressive sub-clinical hemolytic anemia as well as the severe acute types. The mechanism of production of such anemias is unknown. That they do not represent a true idiosyncrasy has been proved by Long and Bliss.[3] The red blood cells in certain individuals may be rendered more susceptible to hemolysis by sulfanilamide because of the existing infection. Because this type of anemia develops in such a large percentage of the patients receiving large doses of sulfanilamide, frequent blood examinations should be made during and following the period of therapy. Patients with severe anemias, requiring sulfanilamide treatment, should be transfused prior to or coincident with the administration of the drug. If severe anemias occur, the drug should be discontinued and the patient transfused.

Leukopenia. In 2 patients (Cases 3 and 4) there occurred marked reductions in the total number of leukocytes (Table 3 and Chart 4). In Case 3 a leukopenia of 1800 was observed twenty-two days after discontinuance of the drug, whereas in Case 4 the leukocyte count fell to 2800 on the twenty-fifth day of therapy. The percentage of polymorphonuclear leukocytes never fell below 43 per cent. The leukocyte counts returned to normal in a few days without the employment of any of the so-called specific forms of therapy. Here, as in the case of the anemia, there was no relation to the amount of the drug given or to the length of time it was administered. The exact mechanism responsible for such leukopenias is as yet unknown. That it is not the same type as results from amidopyrine is suggested by the fact that readministration of the drug to such patients following a return of the leukocytes to normal does not necessarily result in reproduction of the leukopenia.[52] The occurrence of agranulocytosis as well as leukopenia following sulfanilamide therapy has been reported by other workers.[2, 3, 8, 49–56] In some of these cases severe infections may have been a predisposing factor. Allen and Short[57] observed 1 patient with agranulocytosis who made a spontaneous recovery. In a few cases death has occurred.[58–63] These findings suggest the necessity of frequent leukocyte and differential counts during and following the administration of the drug.

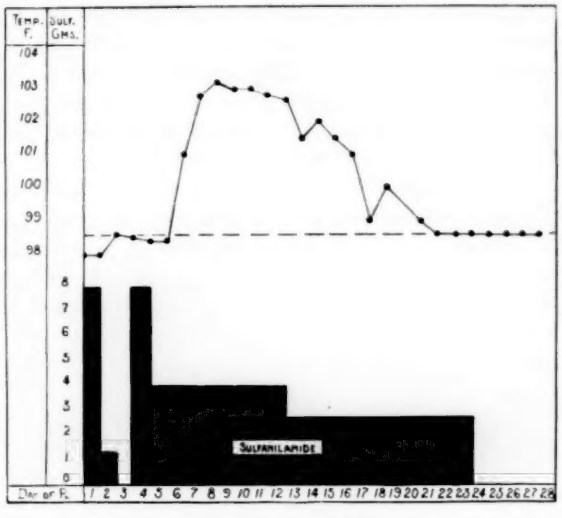

Chart 5. *Case 27.*

This chart illustrates the continuous type of temperature encountered in some patients while receiving sulfanilamide. The temperature always disappears when the drug is discontinued. In this instance it disappeared before the drug was discontinued.

Fever. Six patients (Cases 1, 11, 20, 27, 30 and 31) developed a sustained fever on the fourth or fifth day of therapy, which continued until sulfanilamide was discontinued or the dose was reduced (Chart 5). In Case 20 fever developed on

the fourth day and continued at 102 or 103°F. until the drug was discontinued on the twelfth day. Such febrile responses have been observed by others,[3, 14, 64, 65] and are thought to represent a specific reaction to the drug. Therefore the persistence of fever without clinical evidence of infection should always lead one to suspect that it is due to sulfanilamide. If such is the case, omission of the drug should result in subsidence of the fever.

Skin Reactions. In Cases 20 and 30 a morbilliform rash developed on the fourteenth day of therapy. There was an associated fever, cervical adenopathy, enanthem of the pharyngeal walls, and a palpable spleen. The rash faded twelve hours after discontinuance of sulfanilamide. A much more marked rash was observed in Case 30. Similar skin eruptions have been described.[3, 64–72] They appear during the first or second week of therapy, and disappear twenty-four to forty-eight hours after discontinuance of sulfanilamide.

One patient (Case 5), following exposure to sunlight, developed an erythredema of one side of the face and the dorsal surfaces of the hands and wrists. This reaction disappeared five days later, even though the dosage of sulfanilamide remained unchanged. Previous reports have called attention to similar skin reactions following exposure to sunlight.[66, 68, 71] Because of this risk, it would seem unwise to allow patients receiving sulfanilamide to expose themselves to the direct rays of the sun.

Two patients (Cases 11 and 18) developed generalized urticaria on the tenth day of therapy; in each case it disappeared three days after the omission of sulfanilamide. In Case 18 there was a similar experience three weeks prior to entry, after the giving of 5 gr. of sulfanilamide four times a day for twenty-one days.

Such skin manifestations do not represent serious complications, and require no treatment other than discontinuance of sulfanilamide therapy. The manner of their production is as yet not understood.

Mode of Action of Sulfanilamide

The exact mode of action of sulfanilamide in bacterial infections has not been established. Keefer[6] states that the blood of patients with gonococcal infections becomes bacteriocidal as well as bacteriostatic following the administration of sulfanilamide for a few days. Further studies of this type must be undertaken. That sulfanilamide when administered in large doses has a specific effect on the gonococcus is well demonstrated by the data herein presented.

Similar observations concerning the action of sulfanilamide in streptococcal infections have been made. At the present time it is impossible to say whether or not its dramatic clinical results are due solely to the slightly increased bacteriocidal effect. It is apparent, however, that sulfanilamide therapy offers a method of approach to the study of the conditions responsible for the healing of infectious diseases.

Discussion

From the results obtained in this group of patients it appears that if the highest percentage of clinical cures is to be obtained, sulfanilamide should be administered in large doses. A constant fluid intake should be maintained. It is extremely important that one sixth of the total calculated dose be given every four hours, day and night, if constant blood-sulfanilamide levels are to be maintained throughout each twenty-four-hour period. This method of administration will maintain levels varying from 5 to 10 mg. per cent. If this dose is to be therapeutically effective, definite evidence of improvement should be apparent within forty-eight to seventy-two hours. Those cases that do not experience immediate improvement will not be affected by sulfanilamide therapy until the dose is increased. From our experience this group tends to run lower blood-sulfanilamide levels (5.0 to 7.5 mg. per cent). If this is found to be the case, administration of one third the total calculated dose at two successive four-hour periods, followed by one sixth the calculated twenty-four-hour dose every four hours, will usually suffice to raise the blood-sulfanilamide level above 10 mg. per cent. Such blood levels may prove to be therapeutically effective when the lower levels are seemingly ineffective. Further studies may eventually prove that the highest percentage of cures will be obtained in those patients whose blood-sulfanilamide level is kept at or above 10 mg. per cent.

Despite the fact that striking clinical improvement and sterilization of infected synovial fluids may occur as early as forty-eight to seventy-two hours after institution of sulfanilamide therapy, we have in most cases administered large doses for a period of two weeks or longer in order to obtain the largest possible number of clinical cures. Recent experience suggests that large doses for short periods of time, seven days or less, may suffice. Further studies, however, are necessary in order to establish with certainty that shorter periods of therapy and smaller doses will allow for the same percentage of clinical cures as we have observed. That small doses (10 to 15 gr. three or four times a day, during the day only) may not effect clinical cures is well illustrated by

the 4 patients (Cases 12, 13, 14 and 18) who were so treated prior to hospital entry. The data from these cases further suggest that small doses may increase the resistance of the gonococcus to subsequent sulfanilamide therapy.

Shorter periods of therapy with large doses might aid materially in reducing the frequency of the various toxic manifestations. These, however, except for the rare cases of agranulocytosis, do not represent serious complications, providing they are watched for and recognized early in order that appropriate treatment may be instituted at once. In most cases discontinuance of sulfanilamide and the forcing of fluids (5000 cc. the first day) will suffice. In the case of severe anemias, leukopenia or agranulocytosis, transfusions may be necessary. Frequent urinalyses and serum nonprotein nitrogens — and phenolsulfonephthalein and urine-concentration tests in some cases — have failed to reveal any evidence of renal impairment or irritation following the use of this drug. No evidence of hepatic impairment was noted in any of the cases so studied. In the rare cases with renal impairment requiring sulfanilamide therapy the amount of the drug required must be established by frequent blood-sulfanilamide determinations. In such cases one should aim for a level of 10 mg. per cent.

From our experience in treating gonorrheal arthritis it is obvious that the best end results will be obtained in cases where therapy is instituted before joint destruction has occurred. It is unreasonable to expect prompt and complete subsidence of the soft-tissue inflammatory changes, removal of the fibrosed tissue and restoration of destroyed joint surfaces encountered in the subacute and chronic cases of gonorrheal arthritis. It is quite amazing to witness the restoration to normal of a case of severe acute gonorrheal arthritis so soon after the administration of sulfanilamide. From our data it appears that a gonococcal focus of long duration responds as promptly as does one of short duration. Further study of a large group of patients having infected synovial fluids is necessary in order to establish what percentage can be cured with large doses of sulfanilamide. From the results observed we do not claim that all cases of gonorrhea will be cured, but we believe that early diagnosis and treatment with large amounts of the drug will undoubtedly give the best results.

The specific value of any therapeutic measure can be established only if one is able to demonstrate that the clinical course of the disease is strikingly altered in a large percentage of cases. The results herein reported, as well as those of other workers, indicate clearly the effect of sulfanilamide on gonorrheal arthritis. We have never observed this prompt arrest and subsidence of the inflammatory changes, including joint pain, to take place so regularly with other therapeutic measures, including fever therapy. This quick response of an active gonorrheal arthritis is of itself sufficient to allow one to conclude that sulfanilamide exerts a specific chemotherapeutic effect on the gonococcus.

Additional studies must be undertaken in order to establish (1) the amount of sulfanilamide necessary to cure the majority of the patients with gonorrheal infections; (2) the length of time the drug should be administered; (3) the dose required for those patients who do not respond to the usual dosage; (4) the length of time the drug should be continued in the absence of clinical improvement; (5) whether insufficient initial doses influence the efficacy of larger doses given subsequently; (6) whether some strains of gonococci are sulfanilamide-resistant; and (7) what role the immunologic response of the host plays in the therapeutic effectiveness of sulfanilamide. The answers to such questions will not only increase the usefulness of sulfanilamide therapy, but also will add to our general knowledge concerning the healing of infectious diseases.

SUMMARY

From the results obtained in treating 14 cases of proved and 4 of probable gonorrheal arthritis, 2 cases of gonorrhea, and 2 cases of proved and 2 of probable gonococcal prostatitis, the following conclusions seem justified.

Sulfanilamide administered in large doses for two or more weeks appears to be a specific chemotherapeutic agent for certain strains of gonococci because:

1. Infected synovial fluids can be sterilized in forty-eight to seventy-two hours after institution of therapy.
2. In 17 of the 18 cases having a proved genitourinary focus, no gonococci were found after the third day of treatment. These cases remained clinically cured during the follow-up periods.
3. The gonococcal complement-fixation test failed to become positive in 3 cases of gonorrheal arthritis with infected synovial fluids. In 9 of the remaining 18 cases the complement-fixation test became negative.
4. Nine of the proved and 2 of the probable cases of gonorrheal arthritis showed striking clinical improvement in forty-eight to seventy-two hours after institution of therapy.

5. The end results in the 14 proved and the 4 probable cases of gonorrheal arthritis were more satisfactory and took place in shorter periods of time than occurs with other forms of therapy.

The toxic manifestations resulting from the administration of large doses of sulfanilamide are readily recognized. They do not represent serious complications (except for the hematologic changes), and respond promptly to discontinuance of the drug.

A slow, progressive, sub-clinical hemolytic anemia occurred in 13 of the 28 patients. Leukopenia was observed in 2 cases.

The erythrocyte sedimentation rates fell rapidly in the cases of gonorrheal arthritis showing striking and immediate relief.

The largest percentage of clinical cures will be obtained in patients with gonococcal infections if sulfanilamide in doses sufficient to maintain a blood-sulfanilamide level of 10 mg. per cent or higher for seven or more days is administered early.

The clinical course of rheumatoid arthritis is not affected by large doses of sulfanilamide. The erythrocyte sedimentation rate remained unchanged in 9 of the 10 cases treated.

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PEPTIC ULCER CONSIDERED FROM A SURGICAL POINT OF VIEW*

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THE treatment of patients with peptic ulcer has undergone profound changes since twenty years ago. At that time most physicians, influenced by the enthusiasm of surgeons of an earlier day whose brilliant results with gastroenterostomy had enabled Moynihan[1] to say, "No operation in surgery has produced more striking or swifter results," considered peptic ulcer to be a surgical disease which responded satisfactorily to this form of treatment. Not many years elapsed, however, before other surgical procedures were recommended, for it was soon demonstrated that gastrojejunostomy should not be employed as a routine procedure. Plastic operations on the pylorus, such as the pyloroplasty of Finney and the gastroduodenostomy of Wilkie, gained favor, but after more extensive experience, these too were found to have definite disadvantages. Later, resection of the pylorus and finally subtotal resection of the stomach were developed.

Coincidentally with these changes in surgical procedure, the medical treatment of peptic ulcer developed, so that the management of a high proportion of cases without surgical intervention is now entirely satisfactory. Consequently the treatment of this disease has come to be considered more commonly a medical problem and less frequently a surgical one. In the Massachusetts General Hospital such patients are now followed in a combined medical and surgical clinic.

All these changes in treatment have been reflected in the cases treated at this hospital. Through study of the records of about 2700 cases of peptic ulcer treated here during the last fifteen years, we have reached definite conclusions with respect to the proper surgical treatment of this disease. The indications and types of surgery that have been employed are summarized in the accompanying tables.

The end results of all cases treated by surgery prior to 1923 were appraised by Fremont-Smith and McIver[2] in 1929. At that time, gastroenterostomy was employed as a specific measure. They found that approximately 80 per cent of patients were relieved by this operation. It is of interest that nearly 80 per cent of all ulcer patients seen in this hospital in the fifteen years since 1923 were relieved by medical means (Table 1). It seems entirely possible that the 20 per cent of patients now not rendered symptom-free by medical measures would not have been helped by gastroenterostomy in earlier years.

Table 1. *Type of Treatment Received at the Massachusetts General Hospital (1922-1936) by 2726 Patients with Duodenal Ulcer.*

YEARS	MEDICALLY TREATED CASES				SURGICALLY TREATED CASES	
	NUMBER			PERCENTAGE	NUMBER	PERCENTAGE
	O. P. D.	House	Total			
1922-1926	440	259	699	76.8	211	23.2
1927-1931	322	377	699	80.5	170	19.5
1932-1936	259	481	740	78.2	207	21.8
	Totals		2138	78.4	588	21.6

Within the last fifteen years the percentage of patients requiring surgical treatment has averaged close to 20. The most important evidence presented in Table 1 is that peptic ulcer has come to be regarded as a disease that should be appraised critically in the hospital wards rather

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than be treated solely in the Out Patient Department, as was the case in earlier years.

It is convenient to classify the cases which come to require operation according to the following indications: acute perforation, cicatricial obstruction, profuse bleeding and pain intractable to medical treatment. Although the total number of cases requiring surgery has not changed, a glance at Table 2 will show that the number of patients

Table 2. *Indications for Operation in the 588 Patients with Duodenal Ulcer.*

Years	Indications				
	Acute perforation	Cicatricial obstruction	Profuse bleeding	Intractable pain	Miscellaneous
1922-1926	32	67	6	101	5
1927-1931	55	59	6	45	5
1932-1936	56	67	24	42	18
Totals	143	193	36	188	28
Percentages of grand total	24.3	32.8	6.1	31.9	4.7

operated on for different indications has been greatly modified. Thus in late years the number of patients operated on for so-called intractable pain has diminished by 50 per cent. On the other hand, the significance of massive bleeding as an indication for surgery has been appreciated only recently, and the number of operations for this complication has increased.

ACUTE PERFORATION

It is well established that patients with acute perforation of a peptic ulcer should be operated on without delay. There are a few with small perforations which become walled off spontaneously, either by omentum or by a neighboring viscus, who will survive without operation. The selection of such cases is too difficult at present, and in case of doubt patients should be given a better chance for recovery by early surgical intervention.

The surgery in nearly every case need include no more than simple closure of the perforation. This may be done by placing sutures in normal tissue on either side of the ulcer in such a manner that constriction is avoided, and tying them together. Often this method is impossible because of the size of the ulcer, and it is necessary to use an omental tab to cover the perforation, holding it there by loosely tied sutures passed through the edges of the ulcer. This procedure is highly recommended by Roscoe Graham.[3] He has used it with such success that we are inclined to employ it in all perforations. Constriction of the duodenum rarely occurs when this is done. In any event, it must be recognized that while the pylorus may seem to be obstructed, most of the swelling is due to edema, and a superimposed gastrojejunostomy for relief of the obstruction is very rarely indicated. An attempt to cure the ulcer by means of gastrojejunostomy, pyloroplasty or partial gastrectomy at the time of suture of the perforation is generally considered unjustifiable. Not only are these operations often unsatisfactory, but they add a considerably increased hazard to an already precarious condition. Furthermore, it must be remembered that many patients are cured by the fibrosis of the ulcer which follows perforation and suture.

CICATRICIAL OBSTRUCTION

Obstruction of the pylorus due to peptic ulcer may be produced either by edema due to an active ulcer or by fibrosis and contraction about the pylorus. The distinction is not always easy to make, but is exceedingly important as a means of determining proper treatment. The acute ulcer is usually characterized by the occurrence of typical ulcer pain, in addition to the vomiting characteristic of obstruction. Prompt relief usually follows decompression of the stomach with a Levine tube, a proper diet and the administration of belladonna. Operation is contraindicated in these cases, if it can possibly be avoided, because the extensive periduodenal inflammation prevents any direct attack on the ulcer. If operation cannot be avoided and there is excessive reaction around the duodenum, a conservative operation such as gastroduodenostomy is indicated, in the hope that later a subtotal gastrectomy may be safely done.

On the other hand, there is a large group of patients with pyloric obstruction due to the formation of dense scar tissue, to whom the administration of anti-spasmodics brings no relief. This condition may develop in young patients, but is much commoner in older ones. It is usually associated with low gastric acidity. Gastroenterostomy in this group usually results in complete relief from symptoms, for the simple mechanical problem of pyloric obstruction is answered, and there is practically no danger of late gastrojejunal ulcer.

PROFUSE BLEEDING

Two distinct problems are encountered in this group of cases. One is presented by patients who enter the hospital bleeding profusely, the other by those who have had one or more severe hemorrhages but are in good physical condition at entry.

Treatment of profuse bleeding must be considered without delay. It has been shown from a study of the Massachusetts General Hospital cases by Allen[4] that death occurs in one third of such patients who are fifty years of age or over, but in slightly less than 5 per cent of those under that

age. This difference we attribute to the sclerosis of the eroded vessels in older patients, on account of which thrombosis is accomplished with much more difficulty than in younger ones.

It has also been shown conclusively by Finsterer,[5] and in a small series of cases at the Massachusetts General Hospital,[6] that operation performed more than forty-eight hours after onset of the hemorrhage carries an excessively high mortality. On the other hand, if resection can be done within forty-eight hours there is little more risk than with an ordinary resection. Certainly the mortality will be less in the older age group if they are operated on than if they are allowed to bleed. Younger patients should be treated conservatively, with operation reserved for a later date.

This leads us to a consideration of the patient who has had one or more massive hemorrhages but is admitted with a quiescent ulcer. There is great variation of opinion on this subject. Jordan and Kiefer[7] have shown that such patients are kept symptom-free with extreme difficulty, 40 per cent failing to get relief from medical measures after one hemorrhage, and 85 per cent after two. This group, then, merges with our fourth group of ulcers unresponsive to medical care which require operation.

We conclude from a study of our cases that one massive hemorrhage is an indication for operation in patients over fifty. A single hemorrhage in the younger group demands a careful medical regime. If ulcer symptoms persist, or if a second massive hemorrhage occurs, operation is indicated.

The type of operation to be employed depends on the presence or absence of acute bleeding. A method of approach useful in dealing with acute massive hemorrhage has been described by Allen;[6] in it bleeding is controlled by the finger, while all vessels leading into the ulcer are ligated in normal tissues. If the operation is performed after the subsidence of the acute hemorrhage, a subtotal resection of the stomach should be done. If possible the ulcer should be resected; if not, the vessels supplying it should be ligated. The earlier procedure of gastroenterostomy for massive bleeding has been found to be unsatisfactory.

PAIN INTRACTABLE TO MEDICAL TREATMENT

Although medical treatment of peptic ulcer is much more satisfactory than it was formerly, a certain number of patients still fail to respond to it. Some have persistent pain despite the fact that they are supervised carefully in the hospital. Others improve in the hospital but have a recurrence of symptoms soon after they leave, owing to an unhappy home environment or to excessive business worries. Some find it impossible to continue the proper medical diet outside the hospital. Most of these patients have repeated hospital admissions, surgical intervention finally becoming necessary.

The number of patients classed as intractable to medical treatment is less than half what it was fifteen years ago. In the early years of our survey, posterior gastroenterostomy was employed as a routine operative treatment. Quite obviously many of the successful gastroenterostomies in this group in early years were performed on patients who now might be kept comfortable without surgery. On the other hand, the patients at present classed as intractable comprise one of the most serious challenges to the gastric surgeon; it is here that the poor results of gastroenterostomy are found. Duodenal ulcers on the posterior wall and associated with bleeding, deeply penetrating lesions, multiple ulcers, gastric ulcers that do not decrease in size under treatment, those with an extensive gastritis and those with a high gastric acidity, all demand more than a palliative short-circuiting operation for relief.

The operative procedures heretofore employed in this group of patients are numerous; gastroenterostomy was long the most popular (Table 3).

Table 3. *Type of Operation in the 224 Patients with Duodenal Ulcer Who Were Operated on Because of Intractable Pain or Massive Bleeding.*

Years	Type of Operation		
	Posterior Gastroenterostomy	Resection	Other Operations
1922-1926	87	6	14
1927-1931	37	8	6
1932-1936	20	39	7

Stomal ulcer with its attendant high mortality has occurred so frequently that this operation must be considered entirely unsatisfactory. Pyloroplasty has not been employed in many patients in this series, but where it has been, only temporary relief has often been obtained. Pylorectomy fails to remove much of the acid-bearing portion of the stomach, and it too has proved unsatisfactory. The only procedure that we have found gives relief to a large percentage of these patients is subtotal gastrectomy in which approximately three fifths of the stomach is removed. This is in accordance with the conclusions of many other surgeons, including Finsterer,[5] Berg,[8] Lewisohn,[9] Ogilvie,[10] Marshall and Kiefer[11] and Graham.[12] If it is impossible because of technical difficulties to resect the stomach, Finsterer's "resection for exclusion" may be employed; this is often required in deeply penetrating ulcers of the posterior wall.

The details of subtotal gastrectomy vary considerably with different surgeons. We believe

that this variation is not of great moment. While an adequate follow-up study of such cases cannot be obtained for many years after operation, we know that the patients treated in this manner have furnished exceedingly satisfactory end results. Subtotal gastrectomy following failure of more conservative operations has been required so frequently that we now carry it out as the primary procedure in a great majority of cases. When it is properly performed on patients in the best possible physical condition, the operative mortality is extremely low (Table 4).

Table 4. *Fatalities in 67 Private Patients Who Had Gastric Resections Performed for Peptic Ulcer (exclusive of those operated on late for massive hemorrhage).*

LOCATION OF ULCER	NO. OF CASES	DEATHS
Duodenal ulcer	50	2
Gastric ulcer	10	1
Gastrojejunal ulcer and gastrojejunocolic fistulas	7	0

SUMMARY

The treatment of peptic ulcer has changed markedly in the last twenty years. Prompt surgery is demanded in patients who develop acute perforations, and is occasionally required by an episode of massive bleeding. Thorough medical treatment is indicated in all other cases. Patients who develop cicatricial obstruction do well with gastroenterostomy. Those who develop ulcers which are intractable to medical care or have been associated with massive hemorrhage should receive subtotal gastrectomy.

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SYPHILITIC HEPATITIS WITH JAUNDICE*

Report of a Case

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SYPHILITIC hepatitis with jaundice is an uncommon complication of luetic infections. It occurs in about 1 per cent of cases of early syphilis, and is usually of mild degree. In the secondary stage it is extremely rare but moderately severe. In the tertiary stage it occurs seldom, being reported by McCrae 46 times in 3300 autopsies at the Johns Hopkins Hospital. Thompson has stated that the liver is probably involved in all constitutional syphilis.

Painless afebrile jaundice in a patient with a positive blood test for syphilis presents a clinical problem that is not easy to evaluate. In essence, one must give thought to the various disease entities which may cause this type of jaundice in order to determine whether one or more diseases are present. In making a final diagnosis the past history, present illness, physical examination and all relevant tests must be considered together; no single clinical or laboratory finding is pathognomonic of the cause of jaundice. The question of choice between medical and surgical treatment is often a serious one. Even though the x-ray report of a cholecystogram in such a case is "pathologic gall bladder," this does not necessarily indicate that surgery is the proper treatment.

Most physicians are familiar with the modern accepted methods of anti-syphilitic therapy. To treat a patient who has syphilitic jaundice with arsenic requires a reasonable understanding of pathology and clinical medicine, because, as is well known, this alone may cause jaundice. However, fire sometimes has to be fought with fire, and such a result is no reflection on this method of treatment. All such treatment carries a risk which is relatively very slight, and is accepted by both physician and patient as being far less than that of omitting it.

Most textbooks and articles advise against such treatment. Thompson, Power and Murphy, Osler and McCrae, and others state without qualification that arsphenamine should not be used in the treatment of late syphilitic hepatitis with jaundice.

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Stokes, Wile, O'Leary and a few others assert that the contraindication is relative and not absolute. All authorities agree that potassium iodide should be tried first, but most of them recommend that mercury or bismuth be given next, before trying arsenicals. However, arsenic can be used successfully in the treatment of this type of jaundice, as has been reported by O'Leary, Stokes, Wile, and others, and is demonstrated by the following case.

CASE REPORT

The patient, a 50-year-old, unmarried laboratory technician, was first seen in February, 1935. He complained of afebrile, painless jaundice of 5 weeks' duration. The past history was significant in that he had had rheumatism 15 years previously; the attack began with a sudden onset of sharp pain in the right heel and there were pains in various joints. The patient was in bed for 9 weeks; since then he had had mild rheumatic pains, especially during cold, damp weather; otherwise his general health had been good. He was referred to the New England Deaconess Hospital for study.

The present illness began 6 weeks before admission, when the patient had a moderate "soreness in the bones"; this increased and soon became constant, day and night. At the end of 1 week he quit his work because of loss of strength; after resting at home for 2 weeks he stayed in bed because several joints had become swollen and very painful. Five weeks later his appetite became poor and his strength was quickly depleted on slight exertion. At this time he noticed that his urine was dark. The following day he became jaundiced. He had had no abdominal pain and no complaints which were referable to the gastrointestinal tract. He had lost 10 pounds since the onset of his illness, whereas there had been no previous loss of weight. He had received no medication except aspirin and an alkaline powder; these gave no relief.

Physical examination showed universal deep jaundice and inability to sit up without aid on account of painful joints; practically all the joints were tender, and there was moderate swelling of the knees and wrists. The lungs showed rales at the right base, but were otherwise normal. The heart sounds were regular; the rate was 80 and there were no murmurs. The blood pressure was 120/80. The abdomen showed no tenderness, masses or spasm; the liver was not palpable. The pupils and other reflexes were normal. The other findings were not remarkable.

X-ray photographs were taken of the spine, joints of the extremities, chest and gastrointestinal tract, and intravenous cholecystograms were made. The films revealed a pathologic gall bladder and periosteal proliferation along the internal and posterior aspects of the right ulna; otherwise they were negative.

Laboratory tests showed normal red-cell and white-cell counts, an icteric index of 35 and a blood bilirubin content of 2.1 mg. per cent. Blood Wassermann, Hinton and Kahn reactions were positive on repeated tests. The spinal fluid contained 2 cells per cubic millimeter; the Wassermann reaction was doubtful on the first test and possibly positive on the second. The stools were negative for bile. The gastric contents were negative.

It was apparent that the patient had syphilis and possibly gall-bladder disease. At first it was not clear how much and what kind of treatment he should receive. He was given potassium iodide at once. A surgical consultation was requested, and the patient was seen by Dr. Leland S. McKittrick and by Dr. Elliott C. Cutler. They agreed that in view of all the findings surgery was not indicated. Anti-syphilitic medication was continued; this consisted of potassium iodide and protiodide of mercury given orally, the latter being alternated each week with quinine iodobismuth given intramuscularly.

After 4 weeks in the hospital the patient's condition gradually became worse. At this time he had a severe chill and the temperature fell to 96°F. He developed a diffuse bronchitis, heard over the left chest, and complained of severe pain in both sides of the back, the latter being caused by bilateral pleurisy. There was also severe substernal discomfort, and angina-like pain over the precordia. The blood pressure at this time varied from 75/65 to 110/80; the heart sounds were regular and of fairly good quality. The patient developed auricular fibrillation, which subsided within 48 hours following the use of large doses of morphine and complete digitalization. During the 5th week the patient was no better; the mercury and bismuth were omitted at this time. It seemed reasonable to try arsenic, and 0.1 gm. of neoarsphenamine was therefore administered intravenously; no ill effects were noted. Three days later 0.2 gm. of the same drug was given, after which improvement began. Four days later 0.25 gm. was given. The dosage was gradually increased every 4 days to a maximum of 0.45 gm. From this time on, treatments were given at weekly intervals.

From the 6th to the 10th week the general condition improved. The rales in the lungs gradually subsided and the jaundice disappeared; the patient's appetite returned and his strength increased. In the first part of the 3rd month there was a transient recurrence of auricular fibrillation and edema of the feet. The blood pressure gradually returned to a normal level of 130/80, and the heart continued regular; 0.1 gm. of digitalis was given daily. Ten weeks after admission the patient was able to sit in a chair and walk a little, and was discharged to his home.

During the last 3 years potassium iodide has been given continuously, as well as fifty-six doses of intravenous and intramuscular medication consisting of neoarsphenamine, Mapharsen and quinine iodobismuth; between these doses protiodide of mercury has been given orally. A few months after leaving the hospital the patient developed hypertension, which has persisted to the date of writing at levels of 160/80 to 180/110. He has taken digitalis 0.1 gm. each day. Cardiac decompensation has not recurred. The blood Hinton reaction continued positive during the 1st year, was negative for a short time in the 2nd year and is positive at the present time, although the patient feels very well and presents no special symptoms.

CONCLUSION

The experience of others, together with the results in this case, demonstrates that some patients having syphilitic hepatitis with jaundice can be successfully treated with arsenicals. However, no general rule can be formulated as to which cases may be so treated.

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A NOTE ON DRAINAGE OF THE PREVESICAL SPACE*

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IN MOST suprapubic operations on the bladder the prevesical space or space of Retzius is opened. Practically all urinary surgeons appreciate the importance of drainage of this region, and

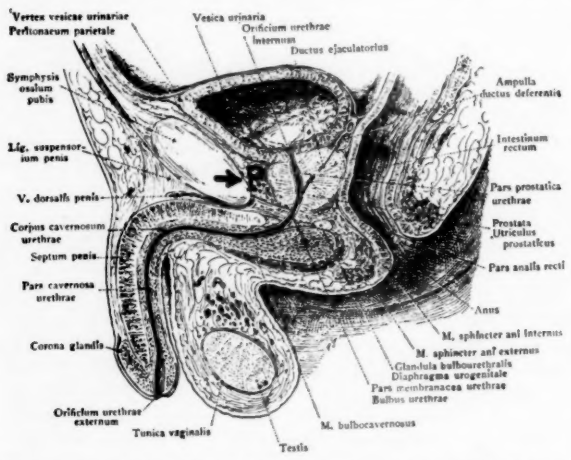

Figure 1. *Median Sagittal Section through the Male Pelvic Organs.*

This drawing shows how the anatomy of the prevesical space, marked P, *makes infection tend to pocket there, once it has gained access. Due to the fascia covering the urogenital pelvic diaphragm below, the pubic symphysis in front, and the prostate and bladder behind and above, this space has very poor natural drainage. There are two paths which extension of infection in this space may take. The first one is laterally on either side around the base of the bladder as far back as the iliac vessels, but this is rather uncommon. The other and commonest path is upward, behind the pubic bone keeping anterior to the peritoneal cavity, to the abdominal wall and the lower end of the suprapubic wound, whence the original infection came.* (Reproduced from Eycleshymer and Jones's *Hand-Atlas of Clinical Anatomy*, by permission of the authors and of the publishers, Lea and Febiger, Philadelphia.)

leave a soft drain down behind the pubic symphysis after every suprapubic operation. However, some surgeons do not realize the importance of leaving the drain in place for a number of days, until the temperature has returned to normal and there is not much discharge, and then withdrawing it a little at a time. Undesirable consequences not infrequently follow when a drain is removed either prematurely or all at once.

Owing to the fascia covering the muscles that form the urogenital pelvic diaphragm, there is no way for the prevesical space to drain dependently; infection therefore tends to remain there, and its spread is promoted because of the loose, fatty tissue which the space contains. Thus it is that premature or precipitate withdrawal of the drain may leave behind a poorly drained septic pocket. This often results in a dirty and slowly healing wound, or even the formation of a slow abscess, which eventually extends by the path of least resistance, namely upward behind the pubic bone to the lower end of the suprapubic wound. Massive pericystic suppuration or periostitis or osteomyelitis of the pubic bone may occur, but fortunately these serious complications are rare.

Two of my cases emphasize the importance of such drainage.

CASE REPORTS

Case 1. The patient, an 84-year-old man, underwent a two-stage suprapubic prostatectomy. A few days after the first stage the drain in the prevesical space was completely removed at one sitting by the intern. There seemed to be no ill effect, except that for some days afterward there was considerable edema of the penis, of probable significance in view of the later events. Two weeks after the first operation the second was done, the prostate being removed through the sinus created by the large suprapubic tube. The wound healed well, but there was abnormal tenderness below the lower end of the wound and a slight fever every evening. Little importance was attached to these sequelae, and since the patient was very anxious to go home he was discharged from the hospital. A few weeks later his doctor telephoned that the lower end of the wound had become very painful, and had finally broken open and discharged a large amount of pus, but no urine. The doctor was advised to open the prevesical space widely and drain it thoroughly for a long time. This was done, and the patient never had any more trouble.

Case 2. The patient, a 64-year-old man, underwent a one-stage suprapubic prostatectomy. Two days after operation, while the hemostatic bag was being removed

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through the suprapubic wound, the drain in the prevesical space caught on the bag and was pulled out with it. The patient's general condition was excellent, but although the suprapubic wound quickly became free of urine it was slow in clearing up and healing. Eventually, however, it healed completely. Two months later the patient began to complain of pain and swelling under the lower end of the suprapubic wound. A fluctuant bulge was opened, a quantity of thick pus was evacuated and a drain was put down in the septic prevesical space. Eventually the wound healed permanently.

In both the cases reported it is evident that the prevesical space became infected at operation, was insufficiently drained and became walled off. After the infection had smouldered there for some weeks an abscess formed, and extended upward along the path of least resistance to the suprapubic region.

The lesson to be learned from these cases is that the prevesical drain inserted after a suprapubic operation on the bladder should not be removed prematurely or all at one time. Its withdrawal should not be started until five or six days have elapsed and the temperature has returned to normal, and the drain should then be shortened a little at a time.

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REPORT ON MEDICAL PROGRESS

STREPTOCOCCAL DISEASE*

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THERE is no denying the fact that hemolytic streptococcal infections are among the commonest of acute infections and cause, in one way or another, a high percentage of the illness in any community. It has been ascertained by the United States Public Health Service in a survey of the respiratory infections that hemolytic streptococcal infections are responsible for at least 5 per cent of the measurable illness and about 20 per cent of all the respiratory diseases. This does not include the cases of acute rheumatic fever or acute nephritis which are initiated by an infection of this type.

Table 1. *Hemolytic Streptococcal Groups.*

GROUP	DISEASE	OTHER SOURCES
A	Human infections: Scarlet fever Puerperal sepsis Rheumatic-fever activity Streptococcal pneumonia	Human nasopharynx and hands Cow's milk
B	Bovine mastitis due to *Streptococcus agalactiae* Human infections (rare): Arthritis Puerperal sepsis	Human throat and vagina
C	Equine strangles and endometritis Bovine mastitis Guinea pig adenitis Human infections (rare): Erysipelas	Human throat, vagina and skin
D	No human infections (?): Endocarditis (?)	Human bowel and vagina Cheese
E	No human infections	Cow's milk
F	No human infections (?): Glomerulonephritis (?)	Human throat and feces
G	No human infections (?) Canine infections	Human throat and vagina Monkey's throat
H	No human infections	Human throat and feces
K	No human infections	Human throat

The normal habitat of the hemolytic streptococcus is in the lymphadenoid tissue of the throat. It does not grow freely on the surface of the mucous membranes but is found in the crypts of the tonsils and in the lymphoid tissue itself. About 30 or 40 per cent of normal individuals carry hemolytic streptococci in their throats at some time during the course of the different seasons of the year, the incidence being highest in the winter and early spring months. The presence of hemolytic streptococci in the human throat may be a transitory phenomenon, or they may be found over long periods of time without causing disease. Carriers are commoner in individuals who are in contact with patients with acute streptococcal infection of the throat, and such contacts are especially liable to become carriers if they have a common cold. Moreover, those who are carriers can spread organisms much easier when they have a cold. For these reasons, anyone with a cold should avoid individuals who have active streptococcal disease, and a carrier with a cold should be careful so that he does not spread infection to other individuals.

In any study of hemolytic streptococcal infection, one will find the following groups: (1) transient carriers; (2) permanent carriers; (3) patients with sub-clinical infection; and (4) patients with clinical infection. To be of any significance it must be determined that the streptococci a carrier harbors in his throat belong to Group A.

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SEROLOGICAL GROUPS AND TYPES OF HEMOLYTIC STREPTOCOCCI

Hemolytic streptococci have been divided and classified according to serological methods into nine groups.[1] These, together with the diseases with which they are associated and with their sources, are summarized in Table 1.

In general it can be said that in so far as man is concerned the vast majority of all infections are due to Group A. This group, in turn, has been divided into twenty-six serological types, but since there has been very little study of such types in the United States, the percentage distribution of various types cannot be stated at the present time. It is true, however, that evidence is lacking to show that the various diseases caused by hemolytic streptococci are produced by any single specific type. For example, Griffith[2] has isolated twenty-three specific types from cases of scarlet fever and of sore throat. This is a subject that requires further study and investigation.

Table 2. *Structure of Hemolytic Streptococcus Group A.*

COMPONENTS	CAPABLE OF PRODUCING ANTIGENIC RESPONSE	REMARKS
Whole organism	Yes	
M substance (protein)	No (haptene)	Type specific
C substance (carbohydrate)	No (haptene)	Group specific
Nucleoprotein	Yes	Not species specific; overlaps with pneumococci and other organisms.
Erythrogenic toxin (A and B)	Yes	Neutralized by antitoxin
Hemolysin	Yes	
Fibrinolysin	No	
Leucocidin	?	

THE ANTIGENIC STRUCTURE OF HEMOLYTIC STREPTOCOCCI

The antigenic structure of human, virulent, Group A hemolytic streptococci is exceedingly complex, and our information concerning it very incomplete. However, a number of various constituents have been isolated and studied. They are summarized in Table 2.

IMMUNITY TO HEMOLYTIC STREPTOCOCCI

So far as is known, hemolytic streptococci are destroyed in the body by means of intracellular digestion. This is greatly facilitated by the presence of specific antibody and complement, which favors and accelerates phagocytosis. There are also good grounds for believing that the macrophage and histiocyte are of greater importance in the destruction of the hemolytic streptococcus than the polymorphonuclear cells. Aside from the immune mechanism which actually destroys the organism, there are other immune bodies that develop during the course of disease. These immune substances neutralize substances produced by streptococci, such as erythrogenic toxin, hemolysin and fibrinolysin, which cause deleterious effects in the body. These antibodies limit the damage done to cells and aid in the localization and fixation of organisms in the tissues.

THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTIONS

Within the last few years there have been a number of advances in the treatment of various hemolytic streptococcal infections. The most important is the use of sulfanilamide. Other methods of treatment, such as immune transfusion, antitoxic treatment and the use of streptococcal filtrates in the treatment of recurrent erysipelas, merit consideration.

Sulfanilamide. There is no longer any doubt that sulfanilamide is the best chemotherapeutic agent so far developed for the treatment of streptococcal infections. In a word, it can be said that this drug has a bacteriostatic (growth-limiting) effect on all strains of human virulent hemolytic streptococci, and for some strains there is evidence that it actually has a bactericidal (killing) effect on small numbers of organisms. It is most effective when antibody is present in the circulating blood, and it appears that the main function of the drug is to slow up the growth of organisms and keep the infection from progressing too rapidly until the normal defense mechanism of the body develops to the stage where there is a positive balance of antibody. In other words, recovery from streptococcal infection following sulfanilamide therapy appears to be due to at least two conditions: first, it is necessary to subject the organisms to a concentration of the chemical that produces maximal bacteriostasis; and, secondly, the body must retain or acquire the power to rid itself of the viable organisms that are producing the disease. In order to produce maximal bacteriostasis it is necessary to give sufficient amounts of the drug so that the concentration in the blood is at least 10 mg. per 100 cc. Antibody is often provided by means of immune-blood transfusions.

The most striking results from sulfanilamide treatment have been obtained in hemolytic streptococcal meningitis, bacteremia, puerperal sepsis, cellulitis, erysipelas, chronic empyema, osteomyelitis and chronic leg ulcer. Less impressive results are reported in scarlet fever and acute tonsillitis, and there is insufficient information available concerning its value in hemolytic streptococcal pneumonia. There is some suggestive evidence that its use reduces the number of cases

of otitis media and mastoiditis following tonsillitis and scarlet fever, but on this more information is necessary before a decision can be reached. In any event, there are good grounds for using this drug in all cases of hemolytic streptococcal infections.

Immune-Blood Transfusion. Several years ago, Lyons[3] recommended the more frequent use of immune-blood transfusions in the treatment of streptococcal infections, especially in cases with bacteremia. The purpose of this method of treatment is to provide antibody which will aid in clearing the blood of organisms and in promoting the localization of the infection. In order that the proper donor may be selected it is necessary to establish that the donor's blood is compatible and that his blood plasma contains antibody which promotes phagocytosis of the patient's organisms. This method has the disadvantage that it requires a trained person to carry out the phagocytosis test; furthermore, in most cases it is necessary to examine a number of donors before a suitable one is found. Nevertheless, it is the best method that is available at present for supplying specific antibody to patients with hemolytic streptococcal infections.

Antitoxic Therapy. Streptococcus antitoxin is capable of neutralizing the erythrogenic and hemolytic toxins of the organism. In some diseases, such as scarlet fever, the erythrogenic toxin is responsible for the eruption and many of the symptoms and signs of intoxication. For this reason, the use of large amounts of antitoxin early in the course of the disease is often followed by the disappearance of the rash, a sharp drop in the temperature and the amelioration of many of the signs of intoxication. Blake[4] has recently stressed the importance of early treatment with antitoxin in adequate doses — 20,000 to 40,000 units, depending on the severity of the case. When this is carried out in cases of scarlet fever, the duration of the disease is shortened, and the course of the disease changed. In view of the frequency of serum sickness, antitoxin should probably be reserved for severe cases of scarlet fever. Antitoxin in erysipelas, puerperal sepsis and other infections has been employed with varying degrees of success. There is no doubt, however, that many of the symptoms of these diseases may be relieved. The antitoxic serum is not curative and one should not expect it to be so, since the effects of the toxin are only a part of the disease process. Nevertheless toxic symptoms add to the patient's difficulties and can be neutralized by the antitoxin, so that the latter should be used in patients with severe signs of intoxication.

The Treatment of Recurrent Erysipelas. One of the outstanding features of erysipelas is its tendency to recur in the same individual. The usual course of events is to observe two attacks coming on within several weeks of one another, but there are numerous instances in which patients may have frequent attacks occurring over a period of months or years. These recurrent attacks may involve the face or the extremities.

While the mechanism for the production of these recurrent attacks is not absolutely clear, there is suggestive evidence that, as a result of a previous hemolytic streptococcal infection which has caused erysipelas, the skin of the involved area becomes sensitized and highly susceptible to the products of the hemolytic streptococcus, so that the presence of hemolytic streptococci in the tissues in small numbers can cause a very acute reaction. In recurrent erysipelas of the face, one can frequently find hemolytic streptococci or staphylococci in the nasal discharge, and often there is evidence of a chronic nasal sinusitis due to these organisms (Stevens[5]). In the case of recurrent erysipelas of the legs, it has been demonstrated by Amoss[6] that hemolytic streptococci invade the tissues from small breaks in the skin that are so often present in epidermophytosis.

It is also known that one does not need hemolytic streptococci in the area of acute inflammation to produce an acute attack of erysipelas, since a recurrent attack can be produced in susceptible individuals by injecting toxic filtrates of hemolytic streptococci into the subcutaneous tissues. For example, if an individual is subject to recurrent erysipelas of the face, an attack can often be produced by injecting a small amount of sterile toxic filtrate into the subcutaneous tissues of the arm. This indicates that the toxic products of the hemolytic streptococci or staphylococci are capable of producing the reaction in susceptible areas of the skin. Naturally in the course of the recurrent attacks there must be a focus of infection in some area from which toxic products are absorbed.

The treatment of recurrent attacks of erysipelas, then, consists of: (1) elimination of the foci of infection, such as chronic nasal sinusitis, and the proper care of the feet; and (2) repeated injections of the patient with the products of the hemolytic streptococcus or staphylococcus. To obtain satisfactory results it is necessary to use both of these methods of treatment.

The treatment is carried out as follows.[5] Hemolytic streptococci and staphylococci are obtained by culturing the nasal discharge. These organisms should be grown in proteose-peptone broth in an atmosphere of carbon dioxide for several days. The culture should then be passed through

a Berkefeld filter, and the filtrate tested for sterility. Subcutaneous injections with the filtrate should be made twice a week, starting with 0.1 cc. of a 1:200 dilution and increasing the amount until 1 or 2 cc. of undiluted filtrate can be tolerated. During these injections a critical dose is often reached, usually between 0.1 and 0.2 cc. of undiluted filtrate, which is followed by swelling of the face or other affected parts. If this amount is reduced the reaction does not recur, and one can then increase the dose gradually so that finally 1 or 2 cc. of undiluted filtrate is tolerated. If the patient can tolerate this amount of undiluted filtrate and if the focus of infection has been removed, the recurrent attacks usually cease. This form of treatment is most satisfactory in a high percentage of cases of recurrent erysipelas or so-called infectional edema of the face.

* * *

Unfortunately there is no effective method of treatment of subacute bacterial endocarditis due to *Streptococcus viridans*. There are isolated cases in which the blood has been temporarily sterilized following the use of sulfanilamide, and rare cases have been observed in which long remissions and the complete absence of symptoms for as long as eighteen months have occurred following the use of the drug. The chief difficulty in the effective treatment of subacute bacterial endocarditis is attacking and destroying the organisms at their source in the heart valves. If one were able to destroy the vegetations so that the organisms would no longer be protected from the action of specific antibodies and leukocytes, the question of recovery would appear to be relatively easy. Very often the blood is sterilized, but the organisms continue to grow in the vegetations and to leave the focus from time to time so that the signs of active infection progress, regardless of a high antibody titer in the blood. This disease remains a challenge to medical investigation, and to effect a cure it appears likely that some method must be devised that destroys the vegetations on the heart valves.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25031

PRESENTATION OF CASE

First Admission. A fifty-year-old, married Greek laborer was admitted because of a discharging sinus over the dorsal spine.

Eight months before entry a small painless swelling appeared on his back between the shoulders in the midline, which he thought was a boil. It remained unchanged after poulticing, and he consulted a physician, who said that it was a cyst and advised removal. After removal the wound healed perfectly within ten days. A few weeks later a second swelling appeared lower down opposite the angle of the scapula and to the right of the midline. This time at an outside hospital a 15 cm. operative incision was made which healed well except for a small sinus opposite the ninth thoracic vertebra. The sinus remained open up to the time of entry and on two or three occasions discharged a small piece of bone. He had felt well and had no other complaints.

For many years he had been a night watchman and later an elevator operator. He was born in Greece but had been in Massachusetts for thirty-two years, although he had returned to the "old country" three times during this period. Since childhood he had had "lumps" in his neck.

Physical examination showed a well-developed and nourished man in no distress. There was a small, healed, non-tender scar on the back of the neck in the midline. At the top of the scar there was a small 5 mm. nodule. Just to the left of the scar, a larger nodule was noted, which was hard, non-tender and freely movable. A 15 cm. scar was present to the right of the midline, extending from the thoracic to the upper lumbar region. In the center of the scar was a very small, non-tender draining sinus. Except for a few carious lower teeth, he was edentulous. Examination of the neck showed a mass 3 by 3 cm. just below the angle of the left jaw, medial to the sternomastoid; it was firm, non-fluctuant, freely movable and non-tender. Examination of the chest was negative. The blood pressure was 138 systolic, 80 diastolic. The abdomen showed bilateral inguinal hernias.

The temperature was 98.8°F., the pulse 100, the respirations 28.

The urine examination was negative. The blood showed a red-cell count of 3,600,000 with 65 per cent hemoglobin, and a white-cell count of 7000 with 65 per cent polymorphonuclears, 28 per cent lymphocytes, 4 per cent mononuclears and 3 per cent eosinophils. A blood Wassermann test was negative.

X-ray films of the spine showed a rounded area of diminished density in the right transverse process of the fifth dorsal vertebra and slight irregularity in the adjoining portion of the rib. The medial portion of the sixth rib in the region of the tuberosity showed increased density and was somewhat irregular in outline. Lipiodol injected into the draining sinus communicated with the area of destruction in the rib. Chest films showed old calcified tuberculosis at each apex.

On the eleventh hospital day he was discharged to his local physician with a diagnosis of chronic osteomyelitis.

Second Admission (four years later). Five months after discharge the patient returned for examination, at which time the sinus had healed. There was good mobility of the spine, and no pain. He was well until three weeks before readmission when the pain recurred in the midline of his back at the site of the old operation. It was aggravated by motion. Four days later he noted a swelling, which became very tender, to the right of the midline on his upper back. He had had no chills or increased perspiration.

Physical examination showed a cervicodorsal kyphosis. There was a tender fluctuant area on the back 3 cm. in width to the right of the midline, extending from the first to the fifth dorsal vertebra. Two small, round, hard nodules were present on the back of the neck just to the left of the midline opposite the fourth and seventh cervical vertebrae.

Examination of the urine was negative. The blood showed a red-cell count of 4,200,000 with 70 per cent hemoglobin, and a white-cell count of 8900.

X-ray films showed a definite variation from normal in the third, fourth and fifth dorsal vertebrae. The joint spaces were hazy and narrow. The heads and necks of the fifth, sixth and seventh ribs showed marked irregularity and contained areas of bone formation and destruction.

On the day of admission an incision was made into the fluctuant area, and 180 cc. of thick, yellow pus was evacuated. The abscess cavity seemed to run upward beneath the muscles over the right shoulder. On the thirteenth hospital day the

wound showed good granulation and the patient was discharged.

Third Admission (seven years later). One year before, he entered the surgical clinic for removal of a "wen" on the right side of his back, which had been present for six years.

He had enjoyed excellent general health until one month prior to his final entry when his urinary stream decreased to a dribble. At the same time constipation increased. One week later he noted numbness and weakness in his legs. He was able to obtain relief at first by vigorous exercise, but this soon became impossible. One week before entry he was unable to stand. At this time he also noted a large mass in the suprapubic region and had a desire to urinate. When he was assisted to his feet he became incontinent to the extent of dribbling. Since then he had not been able to void.

Physical examination showed a depressed scar over the two upper dorsal vertebrae 3 to 4 cm. in depth, in addition to his other scars. Three small movable nodules were present below some matted nodules in the right posterior triangle of the neck. Chest and abdominal examinations were negative except for palpation of the liver edge 2 cm. below the costal margin. The edge was sharp and non-tender. Rectal examination revealed a lax sphincter. The prostate was small, firm and non-tender. The spinous processes of the seventh cervical and first dorsal vertebrae were absent. There was decreased response to all forms of sensory stimuli below the level of the fourth dorsal nerve anteriorly and posteriorly. A spastic paraplegia was present, with the left leg weaker than the right. The knee and ankle jerks were markedly hyperactive, and there was a positive Babinski sign on both sides.

The temperature was 99°F., the pulse 80, the respirations 20.

Examination of the urine showed many clumps of white cells and a rare hyaline cast. No Bence-Jones protein was found. The blood showed a red-cell count of 4,190,000 with 77 per cent hemoglobin, and a white-cell count of 9350 with 70 per cent polymorphonuclears, 24 per cent lymphocytes, 1 per cent mononuclears, 1 per cent eosinophils and 4 per cent basophils. The serum nonprotein nitrogen was 29 mg. per cent, the protein 8.2 gm. A blood Hinton test was negative. A lumbar puncture showed an initial pressure of 130 mm. of water, but combined jugular pressure gave no response. Abdominal pressure caused a rise to 350 mm. The spinal fluid was clear but xanthochromic. It contained 1 lymphocyte per cubic millimeter. The total protein was 378 mg. per cent. The goldsol was 0444333110, the Wassermann negative.

X-ray films of the chest showed mottled areas of dullness in both apical lung fields, especially on the right, with multiple areas of calcification. There were also areas of calcification in both middle lung fields and the soft tissues of the neck. The dorsal spine showed hypertrophic changes. There was no evidence of metastatic cancer. There was partial destruction of the right side of the third dorsal vertebra, with absence of the pedicle in this area. The adjacent portion of the third rib was destroyed. There were cyst-like areas in the medial portions of the second, sixth and seventh ribs and in the fifth, sixth and seventh transverse processes on the right. No deformity of the vertebrae was present which could explain a paraplegia. There was evidence of Paget's disease of the ilium and sacrum on the left side. The skull was negative.

During the first ten days in the hospital the compression damage to the cord gradually increased, and on the tenth day an operation was performed.

Differential Diagnosis

Dr. Alfred O. Ludwig: Apparently there had been some change in the x-ray of the spine at the time of his second entry, as it was beginning to show more involvement of the ribs. May we see the films?

Dr. Aubrey O. Hampton: The x-ray films taken at the time of the first admission are not here. The films that we have show obvious disease in the spine and ribs. The process has extensively involved at least half the dorsal vertebrae, and the ribs adjacent to these vertebrae are surrounded by a fair-sized soft-tissue mass simulating an abscess. The abscess, if it is one, is surprisingly small for so much disease in the vertebra if it were due, let us say, to tuberculosis.

Dr. Ludwig: Is it not unusual for tuberculosis to cause this much destruction without collapse of the vertebrae?

Dr. Hampton: Yes, and the joint spaces of these vertebrae are narrowed but not moth-eaten and irregular as you would expect. There may be destruction in the third dorsal vertebra, but since we cannot see it in the lateral view, we have no proof of it.

Dr. Ludwig: How about other types of infection, osteomyelitis of the spine, for instance?

Dr. Hampton: I do not understand this appearance in the rib. It looks like an expansile lesion on first glance, but I do not believe the rib is actually enlarged. That is the cystic area described, a very curious thing.

DR. LUDWIG: The pictures do not suggest myeloma?

DR. HAMPTON: No, I do not believe it is a tumor. It is probably an infection. The only thing that makes me think of tuberculosis is the calcification in the region; some of it, however, may be in the lung and some in the supraclavicular glands, instead of around the spine.

DR. LUDWIG: Do these findings suggest an actinomycotic infection of the bones of the spine? From what I am able to gather this disease does destroy ribs and transverse processes.

DR. HAMPTON: I think that actinomycosis would be more liable to cause complete destruction in the primary area, with gradual spread instead of spotty destruction such as we have here. The infection in this case skips two ribs and then shows destruction of one at each end of the areas. It is a very unusual picture by x-ray, and I do not know what it is.

DR. LUDWIG: Is there anything to suggest an actinomycotic infection?

DR. HAMPTON: No.

DR. TRACY B. MALLORY: How about infection caused by the typhoid bacillus?

DR. HAMPTON: Any infection could produce this picture.

DR. LUDWIG: I thought I was going to get more help from the x-ray than I did.

To go back to the beginning of this case, it seems to me the first statement we have that might be of some importance is that this man of fifty had had lumps in his neck since childhood. I am inclined to interpret them as being a manifestation of cervical tuberculous adenopathy which existed during childhood but which was inactive at the time of hospitalization. He apparently had pulmonary tuberculosis at some time, with healing and calcification in the region of the old lesion. His recent trouble dates back to eight months before the first entry; then the process went on for eleven years before his last admission here. The most outstanding symptoms were tenderness and constant stiffness in the upper part of the spine, with rather marked pain, nodular swelling and sinus and eventually abscess formation. On the second admission, a very large abscess was found, which contained 180 cc. of pus. Interestingly enough there were few constitutional signs, very little temperature or pulse increase, not very much increase in the white count, very moderate anemia and little weight loss. Then we come to his last admission and another new neurologic symptom. As to the diagnosis of the underlying disease one has to think of tuberculosis, but according to Dr. Hampton's interpretation and from what I know of the x-ray findings in tuberculosis of the spine, these are certainly not the ordinary findings of that condition. From what I am able to discover one sees such changes in actinomycosis, and this disease can produce extensive destruction of the spine without collapse of the vertebrae. However, actinomycosis and blastomycosis are diseases of relatively short duration, — a year or two at the most, — and this has gone on for eleven years.

His final episode is obviously due to compression of his cord, but there seems to be no evidence from the x-ray that such compression is due to a collapsed vertebra.

DR. HAMPTON: I should have mentioned the possibility that he has a secondary infection superimposed on a tuberculous abscess.

DR. LUDWIG: I think it is probably true that when draining sinuses appear in such a case they are almost invariably due to secondary infection. There is one note in the history of a sequestrum's being discharged from a sinus. So far as actinomycosis or blastomycosis is concerned sequestrums are usually absent because large pieces of bone become necrotic. That also holds true of tuberculosis. The spinal-fluid findings, including the gold-sol curve, are characteristic of block, and I believe his neurologic findings are due to extradural abscess formation, with compression of the cord. The serum protein of 8.2 per cent is interesting. Except dehydration I know of only one condition that can cause such a deviation, namely multiple myelomas. I do not know whether it is increased in other types of bone tumors or in amyloid disease, which this man might well have had. He had a liver which seemed to have increased in size at the last entry, when it was found to be 2 cm. below the costal margin. It could not be felt before — at least it was not mentioned. He had none of the other findings of amyloid disease, neither the kidney changes usually giving the picture of nephrosis nor an enlarged spleen. There was only a single determination of the protein so that I am not inclined to place too much importance on that finding. Furthermore, the x-ray findings are not those of multiple myelomas. In this disease there is usually far more anemia than he had and the bone lesions are more often multiple, rather than localized to one small area. Apparently they found Paget's disease in the pelvis on the right side, but I do not see how that could have had anything to do with the situation.

I shall stick to a diagnosis of an infectious process involving the spine, that is, an osteomyelitis, which I do not believe was due to tuberculosis. I do not know what the infectious agent was. Had it been actinomycosis the patient would not have lived so long as he did, and the typical sulfur

granules should have been found. I think the neurologic symptoms of compression of the cord were due to extradural abscess formation, secondary to the infection of the bones of the spine. He had Paget's disease, which I do not believe plays any essential part in the symptomatology.

DR. MALLORY: Are there any suggestions?

DR. WILLIAM J. MIXTER: There is a chance that the patient may have had a perfectly normal space for fluid to pass up and down around the spinal cord without compression of the cord and that the symptoms were the result of a transverse myelitis due to infection.

A PHYSICIAN: Could the spinal-fluid picture be produced by venous thrombosis?

DR. MIXTER: Yes.

A PHYSICIAN: With tremendous increase of blood supply and no place for it to go?

DR. MIXTER: I think so, more probably thrombosis, either arterial or venous, without cord compression. I should guess that it was chronic nontuberculous osteomyelitis, or a secondary process to an original tuberculous focus.

DR. JAMES C. WHITE: As soon as we came down to the posterior surface of the lamina the diagnosis became apparent. Numerous cysts of varied size had worked their way out between the laminae and lay between the bone and muscles. We had thought of the possibility of echinococcus disease, because this man was a Greek, but had not pursued the suggestion. We had also asked about the "wen" that had been removed. He said it was a wen, but in retrospect it is likely that it was an echinococcus cyst. As we cut down through the bone, it was soft and there were a great many cysts between the bone and the dura. There was definite compression of the cord. Furthermore, there was erosion in the pedicles which opened into a large cavity in the extrapleural tissues on the right side. Just how big this area was, I do not know.

CLINICAL DIAGNOSIS

Inflammatory compression of the spinal cord.

DR. LUDWIG'S DIAGNOSES

Osteomyelitis of vertebrae and ribs, with paravertebral abscess and sinus formation.

Extradural abscess.

Compression of the spinal cord.

Paget's disease.

ANATOMICAL DIAGNOSIS

Echinococcus cysts involving vertebrae, extradural space and extrapleural tissues.

PATHOLOGICAL DISCUSSION

DR. MALLORY: I imagine that this was the only Greek who was ever in the hospital on whom an echinococcus complement fixation test was not done. Of course it should have been done. The cyst was very typical and contained daughter cysts and numerous hooklets. There is no question that some of the cysts were secondarily infected, and probably the original draining sinus developed in this way.

DR. LUDWIG: There is no evidence that there was cystic disease anywhere else? How about the lungs?

DR. MALLORY: I think in retrospect the lungs were probably involved.

DR. HAMPTON: I do not believe I have ever seen a cyst in the bone like that.

DR. MALLORY: We know very little about such lesions. Before seeing this case, we did not appreciate that bone could be involved, but in looking the matter up in Kaufmann's textbook, we discovered that involvement of the spine is not uncommon.

DR. THORNTON SCOTT: Coley* reported two cases in 1932.

DR. WHITE: Dr. George W. Van Gorder had a case where the hip bone was involved.

DR. HAMPTON: We have seen it involving bone secondarily but not as a primary cyst in the bone.

DR. MALLORY: The echinococcus test was done afterward and was positive.

CASE 25032

PRESENTATION OF CASE

A six-month-old infant boy entered the hospital for treatment of a cold, running nose and fever of thirty-eight hours' duration.

The child had been well until the morning of the day before entry, when he seemed tired and listless and for the first time in his life had a running nose. That afternoon he vomited on four occasions, bringing up lavender-colored material. A physician was called who found his temperature to be 101°F. and made a diagnosis of a "cold in the chest." The child slept well that night and did not seem to be feverish. He refused his milk but drank some water. The following morning he was very drowsy, although at intervals he became fairly alert. He continued to take water but still refused milk. In the middle of the afternoon his mother gave him an enema because his bowels had not moved for twenty-four hours. A hard stool was obtained, followed immediately by a gush of bright-red blood. The blood was

*Coley, B. L.: Echinococcus disease of bone; report of two cases involving the pelvic girdle. J. Bone & Joint Surg. 14:577-590, 1932.

estimated to be enough to fill a small wine glass. A physician was called and found the child's temperature to be 102°F. He said the child's neck was stiff and advised immediate hospitalization. He was brought into the Emergency Ward that evening. During his illness he had not shown difficulty in respiration and had had no twitchings, convulsions or vomiting, except as noted above.

He had been delivered normally at full term and had apparently steadily gained weight since birth. He had had no previous illnesses. He had six siblings who were living and well. One sibling had died in a "convulsion" at the age of eleven months, and one had died of "suffocation" at the age of six weeks.

Physical examination revealed a well-developed and well-nourished, extremely sick, pale, somewhat cyanotic infant who was too ill to resist attempts at examination. There was slightly diminished resonance over the right chest, with a tendency to bronchial breathing but no rales. The heart was negative. The abdomen was very much distended, with absent peristalsis; it had a doughy consistence and was tympanitic throughout. There was no spasm, and no masses were palpable. There was a bright-red, bloody discharge from the anus, and on rectal examination the examining finger seemed to reach an indefinite mass which slipped away from it.

The temperature was 102.6°F., the pulse 160, the respirations 52.

The blood showed a white-cell count of 14,300. An x-ray film showed no evidence of disease in the chest. There was a large amount of gas in the small intestine, all the loops being slightly dilated; however, there was not marked dilatation of a single loop. In the right lower quadrant there was a beak-like deformity with narrowing at one end.

A laparotomy was performed a few hours after entry.

Differential Diagnosis

Dr. Leo B. Burgin: At the outset we may say confidently that this infant had an acute upper respiratory infection. The nasal discharge, fever and white count are typical. The vomiting may likewise be considered consistent. Infants frequently manifest the presence of infection anywhere in the body by vomiting. Can we attach any significance to the lavender vomitus? It is certainly not blood. Could this represent some foreign material that the infant ingested? Probably not. Such a color might conceivably be due to a reaction between iodine present in frequently used nose-drops (iodine, camphor and menthol) and undigested starch in the stomach. I shall pass it by. The anorexia and drowsiness that occurred during the subsequent twenty-four hours could go very well with the respiratory infection.

At the end of this time a new symptom made its appearance — melena. In determining the source of melena, the nature of the blood as it appears on the outside — that is, whether it is clotted and whether it is pure blood or an admixture with fecal material or mucus — is important. In this instance it is reported as being bright-red blood. Can we tie this up with the respiratory infection? Parenteral diarrheas are not uncommonly seen with respiratory infections. However, we should expect loose watery stools, mucus and, in the case of enteral diarrhea or colitis, pus. This is not the case here. We shall have to look to other causes for an explanation.

Duodenal ulcers occasionally occur, particularly in young infants. Blood, when present, is usually tarry in nature and as a rule well mixed with fecal material; rarely is bright-red blood seen. The vomitus would very likely be described as coffee-grounds or frankly bloody. The peritoneal reaction that was present — distention and a doughy abdomen — and the critical appearance of the infant could suggest perforation. However, most of the findings point to a lesion considerably lower in the gastrointestinal tract.

Henoch's purpura can give bleeding of various types, particularly if the bleeding points be widely separated. In such a case, we might have a combination of tarry stools and bright-red blood. The abdominal findings could be the result of extensive intestinal hemorrhage. However, we should expect to find mention of the typical, associated, purpuric lesions of the skin. Bleeding due to blood dyscrasia of one sort or another or to hemophilia does not appear likely from the history. Congenital telangiectasia involving the gastrointestinal tract might be considered as a possibility. But this is quite rare and usually associated with microscopic bleeding occurring over a long period of time and leading to marked secondary anemia and with a familial history. There is no evidence for it here.

A bleeding rectal polyp could explain some of the findings. The suggestive mass that slips away on rectal examination might represent such a polyp. It should be accessible to proctoscopic examination and would probably be associated with tenesmus and an appreciable outpouring of mucus from the rectal mucosa. This was not the case.

We are left with the consideration of two possibilities: bleeding from a peptic ulcer in a Meckel's diverticulum and intussusception. There are a

number of features which favor either of these diagnoses. The age and sex of this patient are consistent with a diagnosis of intussusception. Usually the previous health is described as good. As in this case, an upper respiratory infection may initiate the intussusception. However, no mention is made of pain which is usually characteristic, coming in bouts as each peristaltic wave tends to push the invaginated intestine onward. On one occasion I saw an eleven-month-old, stoic Chinese infant who had other signs of intussusception but gave no history of pain. The sausage-shaped tumor of intussusception is not described here. The indefinite mass felt by rectum could conceivably be the apex of the intussusception. The doughy consistence of the abdomen, the distention and the absent peristalsis might be due to obstruction and peritoneal reaction attending early gangrene, although the elapsed time was shorter than that usually necessary for such a process to take place. Furthermore, there is no mention of the "currant-jelly" mixture of blood and mucus that is so typical of the disorder, unless we assume that the "bright-red bloody discharge" is a veiled description of such a finding. The clinical signs in the chest could easily have been due to abdominal distention. This was confirmed by subsequent x-ray examination.

We then come to a consideration of Meckel's diverticulum. The symptomatology varies according to whether there is obstruction, inflammation or ulceration, or a combination of these. Bleeding is usually associated with ulceration resulting from the acid secretions of ectopic gastric mucosa in the diverticulum. The bleeding may vary from simple streaks of blood, with or without admixture of fecal material, to frank gross hemorrhage. The bleeding is not attended with any great amount of pain. The diverticulum may be the source of an intussusception. In this event the symptoms of intussusception predominate. The other abdominal findings — doughy abdomen, distention, absent peristalsis, and so forth — may represent evidence of peritonitis due to perforation. In infants with peritonitis a doughy abdomen may be found rather than the typical board-like abdomen. However, this consistence of the abdomen might be due to a large internal hemorrhage. The absence of pain is not of itself an objection to a diagnosis of perforation. Pain is an unreliable symptom in infancy. The x-ray report referring to a "beak-like deformity" in the right lower quadrant I do not comprehend. It does suggest something going on in an area consistent with the location of a Meckel's diverticulum, and I believe that the latter is the diagnosis. There may have been a perforation.

Preoperative Diagnosis

Intussusception.

Dr. Burgin's Diagnoses

Acute upper respiratory infection.
Peptic ulcer of Meckel's diverticulum, possibly with perforation.

Anatomical Diagnoses

Primary intussusception of ileum.
Secondary intussusception of ileum into cecum.

Pathological Discussion

Dr. Tracy B. Mallory: As is often the case, the written summary failed to give a clear impression of the clinical status of the patient. This was a desperately ill infant, and the surgeon, Dr. Robert R. Linton, who was called to see him in consultation immediately after entry noted with alarm the child's complete apathy to all modes of examination. He was evidently more impressed with the mass felt on rectal examination than was Dr. Burgin from merely reading the story, since he committed himself to a diagnosis of intussusception. The patient was prepared immediately for operation with intravenous fluid and a clysis and taken to the operating room.

Exploration showed a double intussusception, evidently primary in the ileum, with secondary intussusception of this mass into the cecum. The secondary cecal intussusception proved readily reducible but the primary one in the ileum was not. The bowel wall showed considerable necrosis, and resection was necessary. The child failed to rally and quietly expired a few hours later. Postmortem examination contributed no further information.

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WHAT SHALL I SUBSCRIBE?

Some time between January 23 and February 7, every man and woman in Greater Boston will be solicited by a representative of the Community Fund Campaign — now an established enterprise in the life of our Metropolitan community. Every physician will have to make up his mind what he will pass on to the support of one hundred and fourteen agencies and federations, comprising more than one hundred and fifty hospitals, health centers and social-service organizations.

Those who have decided that they can and will give money frequently have much difficulty in arriving at a proper figure, and certainly no man can tell them individually what each should give. Thoughtful people, however, want to be intelligent givers and often welcome general information as to some of their colleagues' standards, both as regards motives and amounts.

The charitable works of the profession as a whole and individually in any community are too well known to require comment here. Doctors by the very nature of their education and experience are socially minded. They contribute continuously of themselves. They — at least all but a few of them — believe, moreover, that they should not only give of their time and skill to the medical care of the people, but also contribute of their means to a comprehensive community program that ministers to all sorts of human needs. The great majority of physicians see the necessity of maintaining social and medical agencies as a sine qua non of preserving our present democratic system of life — the American system.

These men, desirous of taking their full share, are sometimes in doubt about the amount they should subscribe. To them should be said: "Determine first what can be easily afforded without sacrifice — then add an amount which entails *some* sacrifice."

A suggested basis of subscription issued by the Community Federation is a scale of giving that is graduated according to income; and from it one gathers that the standard for professional people varies from one per cent up to three per cent of yearly income. The statement, however, adds: "Giving must be adapted to individual circumstances. Some can afford to subscribe on a more liberal basis." If the doctors of Greater Boston can approach these figures, they will go well over the top of their quota, which is $21,555, and thereby help to achieve a much needed oversubscription of the total goal of $4,645,000.

The opportunity of making monthly or quarterly payments cannot be overemphasized. Thoughtlessly a doctor may give a solicitor a ten-dollar bill, hoping that by so doing he will rid himself of further obligation for the rest of the year. Could he be offended if he were asked to give the same amount every month or every three months during 1939?

In other words, each subscriber must answer for

himself these questions: What is my full share of support for this vast and inclusive community program? What should I give throughout the year for service that is continually rendered to the needy?

A BASIS FOR FEE INSURANCE

THAT there is a general movement throughout the country to enable the consumers of medical service, particularly those in the low-income group, to pay their physicians' bills on an insurance basis cannot be denied. Furthermore, the scheme has been approved by organized medicine, with the proviso that all payments should be made in cash and that "agencies set up to provide such insurance should comply with state statutes and regulations to insure their soundness and financial responsibility and have the approval of the county and state medical societies under which they operate," and identical action was taken at the recent annual meeting of hospital administrators.

There remains the necessity for devising ways and means of providing reasonable forms of insurance. It is obvious that a plan which is acceptable in one state is not necessarily one best suited to another section of the country, for fee schedules and types of illness vary geographically. As a result, each state or subdivision thereof must determine the scheme best adapted to meet its particular needs.

The people of Massachusetts have had little, if any, experience with this type of insurance — with the exception of health insurance, as furnished by the old-line insurance companies. It seems reasonable to assume that an organization of the nonprofit variety, under the supervision of physicians, public-health officials and hospital administrators, would be able to furnish adequate care at a lower figure than a commercial company with its overhead charges and its money-making responsibilities.

With this in mind the Associated Hospital Service Corporation is endeavoring to accumulate data in regard to professional fees that will serve to provide a basis for the necessary charges in an insurance scheme to pay physicians' bills. A questionnaire in regard to their bills has been sent to twelve hundred physicians whose patients have had their hospital bills paid in full or in part by the Blue Cross. Already more than five hundred replies have been received. However, a much higher percentage must be obtained in order to provide figures that are representative, and all physicians who have received these questionnaires are earnestly requested to fill them out and forward them at the earliest possible moment.

MASSACHUSETTS MEDICAL SOCIETY

A STATED meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 1, at 10:30 a. m.

Business:

1. Call to order at 10:30 a. m.
2. Presentation of record of last meeting. (Published in *New England Journal of Medicine, 219:* 749-762, 1938.)
3. Reports of Auditing Committee and Treasurer.
4. Reports of standing committees.
5. Reports of special committees.
6. Appointment of delegates.
   a. To the House of Delegates, American Medical Association, for two years from June 1, 1939.
   b. To the annual meetings of the five New England state medical societies in 1939.
   c. To the Annual Congress on Medical Education and Licensure, American Medical Association, at the Palmer House, Chicago, February 13 and 14, 1939.
7. Incidental business.

ALEXANDER S. BEGG, *Secretary.*

Councilors are asked to sign one of the two attendance books before the meeting. The Cotting Luncheon will be served immediately after the meeting.

SECTION OF OBSTETRICS AND GYNECOLOGY

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

POSTPARTUM HEMORRHAGE

The case reports that have appeared in the *Journal* for the past two years have been collected from actual cases occurring in private and general hospital practice. As the different subjects were prepared it was very interesting to observe how easy it was to assemble cases on some subjects and how difficult on others. In fact, some presumably frequent conditions were relatively rare, and vice versa. For example, it was very hard to obtain reports of cases of placenta previa, but very simple to get them of cases of separated placenta. Hence, we believe that the hemorrhage in the majority of cases that bleed in the last few months of pregnancy is caused by some degree of separation of the placenta and that the occurrence of placenta previa of any sort is relatively uncommon. Placenta accreta has become an obstetrical entity solely because of expert pathological examination; it has only been in the last few years that the condition has been recognized, and cases of this sort have been difficult to accumulate. Their actual frequency can be determined only over a period of many years and is dependent on the establishment of adequate pathological departments in all our institutions in which obstetrics is practiced.

The next subject to be discussed is postpartum hemorrhage. We believe that there will be no great difficulty in obtaining cases of this sort. We shall confine the cases to those in which postpartum hemorrhage occurred at the time of labor or within the first few hours after delivery. Bleeding occurring later than this is classified as hemorrhage during the puerperium and will be taken up as a separate topic. The postpartum hemorrhage associated with ruptured uterus and placenta accreta has already been considered and will not be discussed further.

Atony of the uterus resulting in death is fortunately uncommon. Most cases of atonic uteri respond to some form of oxytocic stimulation. We have been brought up on the idea that overdistended uteri, such as those associated with hydramnios and twins, are prone to postpartum hemorrhage. We also connect postpartum hemorrhage with labors that are unduly long or unduly short. The cases that will appear subsequently may or may not bear out these inherited inferences. Postpartum hemorrhage also follows lacerations of the cervix, perineum and vestibule. Bleeding from a laceration of the cervix is not nearly so common in this day of conservative operating as it was in the heyday of accouchement forcé. Postpartum hemorrhage is also associated with partially adherent and partially separated placentas. Illustrations of this sort we hope to find.

In practically all these cases of postpartum hemorrhage the question of transfusion arises. The necessity for obtaining a compatible donor, without too much delay, will be emphasized, and the aftercare of patients who have suffered acute loss of blood at the time of delivery will be considered.

A series of selected case histories by members of the section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the section.

DEATHS

CAHILL — HARRY P. CAHILL, M.D., of 35 Crowninshield Road, Brookline, died January 15. He was in his fifty-sixth year.

Born in Worcester he attended the Worcester schools and Holy Cross College and received his degree from the Harvard Medical School in 1911. He interned at the Boston City Hospital where he eventually became chief of the Nose and Throat Service. When this country entered the War he was doing graduate research work in otology at the University of Basle in Switzerland as a Harvard Fellow. He returned here and entered the Medical Corps of the United States Army and, as a captain, served in France for ten months with the American Expeditionary Forces.

Dr. Cahill was professor of otology at the Tufts College Medical School, assistant professor of otology at the Harvard Medical School and, for many years, surgeon at the Massachusetts Eye and Ear Infirmary.

Among his affiliations were fellowships in the American Medical Association and the Massachusetts Medical Society, and memberships in the American Academy of Ophthalmology and Oto-Laryngology, the American Otological Society and the New England Otological and Laryngological Society. His widow, two sons and his mother survive him.

MARR — EDWARD L. MARR, M.D., of 17 West Wyoming Avenue, Melrose, died December 17, 1938. He was in his sixty-second year.

Born in West Southport, Maine, his family moved to Malden where he attended the local schools. In 1898 he enlisted for service in the Spanish War. He received his degree from Tufts College Medical School in 1910. Dr. Marr had practiced in Melrose for twenty-six years and was .. school physician for fifteen years.

Among his affiliations were fellowships in the American Medical Association and the Massachusetts Medical Society. He was departmental surgeon for the Massachusetts department of the Spanish War Veterans.

His widow, a son, a daughter, a brother and a sister survive him.

PARKER — CHARLES C. PARKER, M.D., of 130 Gallivan Boulevard, Dorchester, died recently. He was in his forty-seventh year. Dr. Parker received his degree from Tufts College Medical School in 1918. He was a fellow of the American Medical Association and the Massachusetts Medical Society.

His widow, a daughter and two sons survive him.

TALBOT — BERTELL L. TALBOT, M.D., of Milford, New Hampshire, died July 14, 1938. He was in his sixty-sixth year.

Dr. Talbot received his degree from the Harvard Medical School in 1896 and was a member of the American Medical Association and the Massachusetts Medical Society.

His widow survives him.

THOMPSON — JOHN S. THOMPSON, M.D., of Antigonish, Nova Scotia, died January 8. He was in his seventy-sixth year.

Born in Antigonish, he attended St. Francis Xavier College in that town and received his degree from Georgetown University School of Medicine in 1895. He served in the navy a short time before beginning medical practice in Cambridge in 1900. Dr. Thompson retired from active practice about eight years ago.

He was a former member of the Massachusetts Medical Society.

A brother, a sister and a niece survive him.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

BLANCHARD — ROSCOE G. BLANCHARD, M.D., of Dover, New Hampshire, died on January 12, 1939, at the age of eighty-six.

He was born in West Cumberland, Maine, in 1853, graduated from Bowdoin College in 1884 and had practiced in Dover since that time.

Dr. Blanchard was a member of the local county and state medical societies and the American Medical Association. He was prominent in various Masonic bodies.

VERMONT STATE MEDICAL SOCIETY

VERMONT DEPARTMENT OF PUBLIC HEALTH

The following communicable diseases were reported to the office of the Department of Public Health during the month of October: chickenpox, 204; measles, 8; undulant fever, 2; scarlet fever, 19; typhoid fever, 4; whooping cough, 220; mumps, 42; lobar pneumonia, 3; German measles, 6; Vincent's infection, 6; tuberculosis, 9.

The Laboratory of Hygiene made 2551 examinations, the details of which are:

Examinations for diphtheria bacilli	112
" " typhoid fever (Widal reaction)	50
" " undulant fever	117
" " gonococci in pus	121
" " tubercle bacilli	231
" " syphilis	1257
" of water, bacteriological	227
" " water, chemical and bacteriological	156
" " milk, market	133
" " milk, submitted for microscopic only	2
" " foods	27
" for courts, autopsies	3
" " courts, miscellaneous	34
Autopsies to complete death returns	3
Miscellaneous examinations	78

The director of the Division of Venereal Diseases reports 20 cases of gonorrhea and 59 cases of syphilis. Eleven speaking trips were made, chiefly to parent-teacher groups and to high schools.

The director of the Crippled Children's Division reports a total of 158 visits made by nurses and the social worker. At the beginning of the month, 6 patients were in hospitals, 9 were admitted and 12 discharged. Nine patients were in convalescent homes at the beginning of the month, and 1 patient was discharged from Warm Springs, Georgia. Fifty-six pieces of apparatus were fitted, 24 orthopedic corrections were made to shoes, and 2 pieces of apparatus were repaired. The occupational therapy director reports sales for the month of $78.50.

The Public Health Nursing Division reports the opening of a new unit for Morristown and Stowe on October 15, with headquarters in Morrisville. Conferences and committee meetings took up the greater part of the month and the director spoke before ten of the county home-demonstration finish-up meetings.

The director of the Maternal and Child Health Division attended the meeting of the American Dental Association in St. Louis, also the meetings of the American Public Health Association and the American Pediatric Society. Six hundred and forty-seven baby booklets, 300 diphtheria consent cards and 451 notifications of birth registration were sent out during the month.

MISCELLANY

COMMUNITY FUND CAMPAIGN

During hard times — whether of "depression" or "recession" — and their years of aftermath, there has been a greater call for free and partially free medical and hospital services.

Statistics are not dry when they reveal that in the past three years the number of patients given free or low-price hospital and clinical care in those Metropolitan-district health services that receive aid from Greater Boston's Community Fund has almost doubled.

That the burden on the hospitals is excessive may be gleaned from the fact that last year member hospitals of the Greater Boston Community Federation used nearly $100,000 from their endowment funds to meet current expenses of care for destitute and low-income persons. The 114 agencies and federations participating in Greater Boston's 1939 Community Fund Campaign give not only hospital, dispensary and clinical services, but convalescent, maternity and home-nursing care. There are social services for old and young, the deaf and the blind; services to give the underprivileged a fair chance in life; services designed to turn delinquency into constructive citizenship; services to train the handicapped to compete on an even basis with normal persons. Every phase of human well-being is within the Federation's scope, with much of it devoted to preventive medicine. Yet the health needs of the destitute and low-income groups are not adequately met — a serious fact, not only for them but for the general health and economic strength of the whole community. In fact, if only to promote the general safety, wholesomeness and stability of community life, the valuable constructive work of all the agencies should be strengthened.

The three-year-old Federation has been going steadily forward in its efforts to bring the agencies up to adequate support, after their years of reduced income due to depression. Because of this, and because more organizations are in the campaign this year, more givers and larger subscriptions are needed for Greater Boston's Community Fund Campaign, which, starting January 23, extends through February 7. Looking forward to a generous oversubscription of the minimum goal of $4,645,000, Stuart C. Rand, general chairman, and every member of his able

corps of assistants are asking all citizens to "give till it feels good."

Each year the medical profession has been asked to pledge of its means, despite the fact that every day of the year the doctor gives freely of his services to many from whom he can never hope to obtain a cent. The doctors have responded, perhaps because they are so accustomed to answer the call of human need that the Community-Fund appeal finds their hands automatically reaching for a pen to sign a subscription.

Few, if any, physicians feel that their free work entitles them to exemption from the Community Fund call, no more than it exempts thousands of other volunteers who give generously of their time and energy throughout the year to the work of social-service agencies. Physicians and surgeons know, too, that hospitals, clinics and convalescent institutions give young members of the profession experience and training they could get nowhere else; and that they may bring their private patients to these institutions for the benefit of the judgment and skill of the older men who are the attending physicians and surgeons and for the use of the highly specialized and expensive equipment that would not otherwise be available were it not for the whole-hearted support of such institutions by the community.

This year's group of one hundred and seven doctors lending their efforts to make the 1939 Community Fund Campaign a success is headed by Dr. William B. Breed. The ten subcommittees are as follows:

Vice-chairman, Dr. Herrman L. Blumgart. Committeemen: Drs. Charles H. Bradford, Newton C. Browder, John G. Downing, Henry E. Groden, Abraham Myerson, Max Ritvo, Virgil G. Casten, Hugh C. Donahue, Edward Harding, Francis Rouillard.

Vice-chairman, Dr. Earle M. Chapman. Committeemen: Drs. Hollis L. Albright, Frank E. Barton, G. Marshall Crawford, Allen P. Joslin, John V. Leech, Alexander Marble, Thomas H. Peterson, Samuel N. Vose, James K. Wardwell, Richard G. Whiting.

Vice-chairman, Dr. R. Cannon Eley. Committeemen: Drs. Goeffrey Edsall, Louis K. Diamond, William T. Green, Randolph K. Byers, Henry E. Gallup, F. William Marlow, Jr., Robert Sanderson.

Vice-chairman, Dr. Marshall N. Fulton. Committeemen: Drs. James M. Baty, Edward M. Cole, Lowrey F. Davenport, Eugene C. Eppinger, John P. Hubbard, T. Duckett Jones, Robert T. Monroe, William T. Salter, Reuben Z. Schulz, Harry A. Warren.

Vice-chairman, Dr. Robert J. Joplin. Committeemen: Drs. Perry C. Baird, Jr., Richard Chute, Walter E. Garrey, Jeremiah E. Greene, Sylvester B. Kelley, G. Douglas Krumbhaar, Lendon Snedeker, J. Sydney Stillman, Thomas V. Urmy, Charles B. Kimmel.

Vice-chairman, Dr. Alfred O. Ludwig. Committeemen: Drs. Donald V. Baker, John W. Cass, Jr., Howard C. Coggeshall, John R. Frazoo, Ward I. Gregg, Alfred Kranes, James H. Means, Michael E. Murray, Paul Norton, John W. Zeller.

Vice-chairman, Dr. William B. Stevens. Committeemen: Drs. John A. Abbot, Louis Arkin, William Dameshek, Julian C. Gant, Joseph Lentine, Jacob Lorman, Walter S. Levenson, Jacob H. Swartz, George S. Speare, Abraham Rudy.

Vice-chairman, Dr. Charles L. Swan, Jr. Committeemen: Drs. Arthur Berk, Benedict F. Boland, James E. Fish, Ashton Graybiel, Reed Harwood, Eugene E. O'Neil, Clifford C. Franseen, Weston T. Buddington.

Vice-chairman, Dr. Soma Weiss. Committeemen: Drs. Leo Alexander, Seth F. Arnold, Austin M. Brues, John T. Edsall, Maxwell Finland, George E. Heels, Franc D. Ingraham, Paul Kunkel, G. Kenneth Mallory, Merrill C. Sosman.

Vice-chairman, Dr. Greene Fitzhugh. Committeemen: Drs. Henry Clifford, Benjamin Cornwall, Moses Lurie, Bretney Miller, John P. Monks, John L. Newell, Langdon Parsons, Somers Sturgis, Milton Thompson, Claude E. Welch.

TRICHLORETHYLENE DEGREASERS

A common method of cleaning metal objects coated with oil, grease or similar substances is by means of an organic solvent applied in a degreaser. The usual degreaser is a tank suitable in size to the work, in which the solvent is heated to boiling at the bottom and the vapor subsequently condensed by water cooling at a higher level. Trichlorethylene is the solvent almost universally used. Questions as to the effect of such a machine on the health of workers employed in its vicinity are frequently raised.

When idle, even though the tank be open, the escape of vapor from a properly adjusted degreaser is not great unless there is a strong current of air over the top of the tank. The introduction and removal of objects into and from the machine greatly increase the escape of solvent vapor. It has been found, however, that small and medium-sized degreasers, properly operated and not overloaded, do not constitute an important health hazard, even when used continually, provided that they are placed in a reasonably well-ventilated room. Larger machines — those of over 12 square feet cross-sectional area — may on the other hand subject the operator to high concentrations of solvent vapor, especially if used continually. The cleaning out of degreasers, particularly those in which the worker must enter the tank in the process, may involve exposures to very high concentrations of trichlorethylene vapor for limited periods of time.

Trichlorethylene vapor in high concentrations will cause unconsciousness and even death, but the ill effects of repeated exposure to small concentrations are apparently less severe than those of most other chlorinated hydrocarbons. Much of the trouble caused by trichlorethylene in the past has been attributed to impurities not present in the product now commercially available. Continuous exposure to concentrations too low to cause immediate effects, such as headaches and dizziness, may nonetheless eventually injure the worker. Addiction to trichlorethylene not infrequently follows continued exposure to high concentrations of vapor.

The following rules for the safe operation of degreasers are advised:

1. Place the degreaser in a high-posted, good-sized room, if possible. If only a small room is available, install one or more window fans to improve the general ventilation.
2. Be sure that there is an adequate supply of cooling water for the condenser of the degreaser.
3. Never allow the machine to be so overloaded that the vapor line rises above the condenser tubes.
4. Make sure that the process of cleaning out the tank does not involve an excessive exposure to solvent vapor. This can usually be accomplished by airing out the machine after withdrawal of the liquid, but additional precautions may sometimes be necessary. Cartridge respirators do not give adequate protection if the exposure is heavy. Hose masks or air-line respirators may be used if they do not impede the worker too greatly.

5. Local exhaust ventilation, through slots along the edges of the tank, should be necessary only in extreme cases. Such ventilation will reduce the concentration of solvent vapor in the air but is likely to increase the loss of solvent.
6. If the odor of the solvent persists in the vicinity of the machine, or if workers complain of ill effects, notify this office and ask for an air analysis. The atmospheric concentration of trichlorethylene vapor should not exceed 200 parts per million parts of air.

Division of Occupational Hygiene, Massachusetts Department of Labor and Industries.

NOTES

Dr. Riley H. Guthrie, chief executive officer of the Boston Psychopathic Hospital, has been appointed first assistant physician at Saint Elizabeths Hospital, Washington, District of Columbia, it has been announced by Dr. Winfred Overholser, superintendent of the hospital. Dr. Guthrie received the degree of Doctor of Medicine from the University of Tennessee School of Medicine in June, 1921. He served on the staff of the State Hospital at Little Rock, Arkansas, for three years, spent two years in private practice, and then resumed institutional work as assistant physician at the State Hospital at Massillon, Ohio. Following this he was appointed medical officer at the Boston Psychopathic Hospital, serving for one year, and for six years thereafter was assistant superintendent of the Monson State Hospital at Palmer, Massachusetts. In June, 1935, he was appointed assistant to the Commissioner of Mental Diseases of Massachusetts, and in November of the same year chief executive officer of the Boston Psychopathic Hospital. He is a diplomate of the American Board of Psychiatry and Neurology, and has contributed extensively to the literature of psychiatry. In a recent country-wide competitive examination held by the United States Civil Service Commission he received the highest rating given.

Middlesex University announces the appointment of Dr. Louis Bergmann, of Vienna, to a full-time teaching position in the School of Medicine, as associate professor of anatomy. Dr. Bergmann received his M.D. degree from the University of Vienna, where he served as assistant to Prof. Julius Tandler in the anatomical department. He accompanied Prof. Tandler in 1934 to China, where he was associated with the National Medical College of Shanghai and taught anatomy at the Hunan Yale Medical College in Changsha and at the Army Medical College in Nanking.

CORRESPONDENCE

TRANSFUSION OF INCOMPATIBLE BLOOD

To the Editor: Your editorial and the letter from Dr. Dameshek, printed in a recent issue of the *Journal*, calling attention to the dangers of incorrect blood grouping, surely come at an opportune time. I should like to express my agreement with your opinions, and also call attention to other dangers of a slightly different sort which may result from incompetent blood-group determinations.

It seems to me that part of the trouble is traceable to the lack of properly qualified experts in this field. This in turn is perhaps due to the fact that blood grouping, though recognized as important, is scientifically treated as a sort of stepchild, often being taught as a part of some subject not closely related. There are no chairs of blood grouping in our schools, and it is difficult for a person whose research has been chiefly concerned with blood grouping to get an academic position, unless he has a second string to his bow. Consequently there is little financial stimulus for promising young men to devote themselves to the study of this important, and fascinating, subject. This is in unfortunate contrast to the situation which prevails in some foreign countries, for example, the U. S. S. R., where the chief cities have institutes specifically devoted to the study of blood groups and blood transfusion.

It is perhaps not necessary that all routine blood-group determinations be carried out by experts who have spent years in a study of the subject, though it would certainly be desirable that the work be done by persons with better training than that now routinely available. But it would seem highly important that such experts be available, at least one in every city, so that their advice could be sought, as in the preparation of serum and in the not-too-infrequent cases of peculiar reactions encountered in blood grouping.

In one such case, a young man who claimed that his blood group had changed from Group O to Group A was retested in my laboratory, with the result that he was found to belong to the weakly reacting type of Group A, designated A_2. It is well known that some Group B serums may lack (or lose after brief storage) the agglutinin for this type of blood, so it is likely that the technician in the first hospital (one of the large hospitals in this city) used such a serum and wrongly classified the young man as belonging to Group O. The startling thing about this story is that, according to his own account, the young man had been used twice as a donor, under the impression he belonged to Group O!

It is probably no exaggeration to say that not one in fifty of those who routinely attempt to determine blood groups could give an intelligible account of the sub-groups A_1 and A_2, of the independent blood types M, MN and N, or of the possible kinds of irregular reactions. In 99 cases out of 100, this knowledge is not needed, but in the hundredth case it may mean the difference between life and death for the patient.

A further danger to the public lies in the fact that many grossly unqualified persons are willing to constitute themselves "experts" in this important field, when as a matter of fact they are almost entirely without training in it. It should be emphasized that the possession of a medical or Ph.D. degree, or even a lifetime of experience in some other branch of medical science, does not constitute a person an expert in blood grouping, which is itself a special and intricate subject, with its own discipline and large body of literature.

It is to be hoped that something can be done to remedy this situation; perhaps departments or even whole institutions devoted to the study of this important subject will ultimately be established. In the meantime it would seem that the least that can be done is to come to some sort of agreement as to the qualifications which a person must possess before being permitted to carry out clinical blood-group determinations and what qualifications constitute an expert in the subject.

WILLIAM C. BOYD, Ph.D.

Boston University School of Medicine,
Boston.

NOTICES

ANNOUNCEMENT

EDWARD S. STONE, M.D., announces the opening of an office at 416 Marlborough Street, Boston.

MEDICAL CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 p. m. on Thursday, January 26, in the amphitheater of the Peter Bent Brigham Hospital, Dr. Samuel A. Levine, assistant professor of medicine, Harvard Medical School and senior associate in medicine, Peter Bent Brigham Hospital, will give a medical clinic. Practitioners and medical students are cordially invited to attend.

WINTHROP COMMUNITY HOSPITAL

The next meeting of the staff of the Winthrop Community Hospital will be held at the hospital on Thursday evening, January 26, at 8:30.

Dr. Joseph H. Burnett will speak on "Fractures and Sprains of the Ankle Joint: Their diagnosis and treatment." The talk will be illustrated by practical demonstrations.

Nurses and medical students are cordially invited to attend.

J. J. ABRAMS, M.D., *Secretary.*

SYMPOSIUM ON THE PUBLIC-HEALTH SIGNIFICANCE OF THE VIRUS AND RICKETTSIAL DISEASES

The faculty of the Harvard School of Public Health is offering a short course of lectures, clinics and demonstrations on the virus and rickettsial diseases, with special emphasis on their public-health significance, to be held at the school during the week of June 12-17, 1939. Lectures on the etiology, epidemiology and methods of control of these diseases, given by members of the faculties and by former students of the Harvard School of Public Health and of the Harvard Medical School, will occupy five mornings. Special clinics and demonstrations will be given each afternoon. In some instances these demonstrations will be continued through the week, so that all the members of the symposium can attend. On the last morning, a panel discussion will be held on the three main topics presented in the symposium.

The fee for the course will be $25.00, payable at any time up to June 12. Enrollment, however, should be arranged before June 1, as facilities for many of the clinics and demonstrations are limited. The lectures will be published later in a single volume, which will be sent to each person who has registered for the course.

Further information may be had by writing to the Secretary of the School of Public Health, 55 Shattuck Street, Boston.

ROBERT B. BRIGHAM HOSPITAL

There will be an open meeting at the Robert B. Brigham Hospital, 125 Parker Hill Avenue, Roxbury, Tuesday evening, February 7, at 8:00.

Dr. Loring T. Swaim will give an illustrated talk on "Prevention and Correction of Deformities in Chronic Arthritis."

All doctors and medical students are cordially invited to attend.

EDITH I. COX, *Superintendent.*

SUFFOLK DISTRICT MEDICAL SOCIETY

There will be a meeting of the Suffolk District Medical Society at the Boston Medical Library, 8 Fenway, on Wednesday evening, January 25, at 8:15.

PROGRAM

A DISCUSSION OF RECENT PROGRESS IN DIABETES
(arranged by Dr. E. P. Joslin).

Résumé of the Diabetic Situation Here and Elsewhere. Dr. E. P. Joslin.
Treatment with Diet and Protamine-Zinc Insulin in Hospital and Home. Dr. A. P. Joslin.
Crystalline Insulin. Dr. Alexander Marble.
Diabetic Coma. Dr. Howard F. Root.
Peculiarities in Therapy of Diabetic Children on Two Continents. Dr. Richard Wagner.
Hypoglycemia. Dr. Henry Baker and Dr. Alexander Marble.
A Resurvey of Dr. Harvey Cushing's Patients with Acromegaly and Young's Experimental Pituitary Diabetes. Dr. Howard F. Root.
Thirty-Nine Pregnancies in Diabetics in 1938 and Studies Thereon. Dr. Priscilla White.
The Emphasis Shifts from Treatment to Prevention and Early Detection of Diabetes. Dr. E. P. Joslin.
The Future. Dr. E. P. Joslin.

JOHN P. MONKS, M.D., *Secretary.*

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the auditorium of the Joseph H. Pratt Diagnostic Hospital, Bennet Street, at 12 o'clock noon, Wednesday, January 25; Dr. Hilbert F. Day will preside. Dr. Samuel Proger will direct inspection of the new hospital either before or after the program. Miss Frances Stern will present a dietetic exhibition.

PROGRAM

Pancreatic Enzymes. Dr. Joseph H. Pratt.
Lesions About the Pylorus. Dr. Jacob J. Schloss.
Hemorrhage Due to Peptic Ulcer. Dr. Henry H. Lerner.
Chronic Duodenal Ileus. Dr. Katherine S. Andrews.

C. W. MCCLURE, M.D., *Secretary.*

MASSACHUSETTS PSYCHIATRIC SOCIETY

There will be a meeting of the Massachusetts Psychiatric Society at the Boston Psychopathic Hospital, Friday evening, January 27, at 8:00.

Judge John F. Perkins of the Boston Juvenile Court will speak, and Drs. Abraham Myerson and Kenneth J. Tillotson will present a paper "Theory and Practice of the Total-Push Method in Schizophrenia."

W. FRANKLIN WOOD, M.D., *Secretary.*

BOSTON MEDICAL LIBRARY

The annual meeting of the Boston Medical Library will be held in Sprague Hall at 8 Fenway, Tuesday afternoon, January 24, at 4:30 o'clock. Reports will be received from the Board of Trustees, the Treasurer, the Librarian and from the various committees. Two vacancies on the Board of Trustees are to be filled.

All fellows of the Library are urged to attend.

JAMES M. FAULKNER, M.D., *Secretary.*

NORFOLK DISTRICT MEDICAL SOCIETY

A regular meeting of the Norfolk District Medical Society will be held in the Evans Auditorium of the Massachusetts Memorial Hospitals, 78 East Concord Street, Boston, on Tuesday evening, January 31, at 8:30.

PROGRAM

Erythroblastosis Foetalis. Dr. H. C. Petterson.
Presentation of a Case of Osteomyelitis of the Frontal Bone. Dr. L. F. Johnson.
Demonstration of Technic Employed in the Placental Block Bank. Dr. F. E. Barton.
Cardio-omentopexy for Revascularization of the Ischemic Heart. Medical — Dr. Ashton Graybiel. Surgical — Dr. J. W. Strieder.
Hyperthyroidism and Heart Disease. Dr. H. M. Clute.

FRANK S. CRUICKSHANK, M.D., *Secretary.*

ARLINGTON AND BELMONT MEDICAL CLUBS

A combined meeting of the Arlington and Belmont medical clubs will be held at Hambury Hall, Ring Sanatorium and Hospital, on Tuesday evening, January 24, at 8:00.

The report of a study on "The Use of Insulin in Toxic Hallucinosis" will be presented by Drs. Hosea W. McAdoo and Curtis T. Prout of the Ring Sanatorium staff.

Following the program a buffet supper will be served.

MICHAEL F. NIGRO, M.D., *Secretary,*
Arlington Doctors' Club.

LEO A. BLACKLOW, M.D., *Secretary,*
Belmont Medical Club.

SALEM HOSPITAL PUBLIC-HEALTH LECTURES

The Salem Hospital will conduct a series of Sunday afternoon lectures this winter on medical subjects of general public interest. The purpose of these lectures is to afford the layman an opportunity to gain an accurate knowledge of methods for the protection of his health and the prevention of illness.

The lectures will be free to the public and will be held in the auditorium of the Nurses' Home during January, February and March, at 4:00 p. m. The first lecture was given January 15 by Dr. Walter G. Phippen, who spoke on "Liver Complaint and Gall-Bladder Disease."

The remainder of the program is as follows:

January 22. Skin Evidences of General Ill Health. Dr. E. Lawrence Oliver.
January 29. How Are Your Kidneys? Dr. Henry D. Stebbins.
February 5. Your Teeth. Dr. Edgar A. Wright.
February 12. The Position of X-Ray in Present-Day Medicine. Dr. Stanley A. Wilson.
February 19. Watch Your Diet. Miss Edith L. Hoadley.
February 26. The Health of the Pre-school Child. Dr. Robert T. Moulton.
March 5. Why Nerves? Dr. William V. McDermott.

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology announces an important change in its methods of examination of candidates for the board's certificate.

Examinations will be divided into two parts. Candidates whose applications are accepted will be required to pass a *written* examination which will be held simultaneously in various cities throughout the country approximately sixty days prior to the date of the *oral* examination.

The *written* examination will include all the subjects previously covered by the practical and oral examinations.

Oral examinations will be held at the time and place of the meeting of the American Medical Association and of the American Academy of Ophthalmology and Otolaryngology, and occasionally in connection with other important medical meetings. The *oral* examination will be on the following subjects: external diseases, ophthalmoscopy, pathology, refraction, ocular motility, and practical surgery.

Only those candidates who pass the *written* examination and who have presented satisfactory case reports will be permitted to appear for the *oral* examination.

Examinations scheduled for 1939: *written,* March 15 and August 5; *oral,* St. Louis, May 15, and Chicago, October 6.

Applications for permission to take the *written* examination March 15 must be filed with the secretary not later than February 15.

Application forms and detailed information should be secured at once from Dr. John Green, secretary, 6830 Waterman Avenue, St. Louis, Missouri.

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held on Tuesday, January 24, in the Peter Bent Brigham Hospital amphitheater (Shattuck Street entrance), at 8:15 p. m.

PROGRAM

Presentation of cases.
Some Clinicoroentgenological Correlations. Dr. Merrill C. Sosman and Dr. Samuel A. Levine.

Medical students and physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, JANUARY 23

MONDAY, JANUARY 23

8:15 p. m. New England Heart Association. Boston City Hospital, Mallory amphitheater.

TUESDAY, JANUARY 24

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. X-ray demonstration. Dr. Alice Ettinger.
*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.
4:30 p. m. Boston Medical Library, annual meeting. Sprague Hall.
*8:15 p. m. Harvard Medical Society. Peter Bent Brigham Hospital, amphitheater (Shattuck Street entrance).

WEDNESDAY, JANUARY 25

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.
*12 m. Clinicopathological conference. Children's Hospital amphitheater.
12 m. Boston Gastroenterological Society. Auditorium of the Joseph H. Pratt Diagnostic Hospital, Bennet Street, Boston.
8:15 p. m. Suffolk District Medical Society. Boston Medical Library.

THURSDAY, JANUARY 26

8:30-9:30 a. m. Exchange visit, Surgical and Orthopedic Staffs of the Peter Bent Brigham and Children's hospitals, held this week at the Children's Hospital Orthopedic.
*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Medical social-service case presentation. District Service and Social Service Staff.
*3:30 p. m. Medical clinic at the Peter Bent Brigham Hospital.

FRIDAY, JANUARY 27

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. **Examination of Coronary Circulation by the Injection of a Radio-Opaque Substance.** Dr. F. T. Fulton.

*10 a. m. - 12:30 p. m. Tumor clinic. **Boston Dispensary.**

8 p. m. Massachusetts Psychiatric Society. **Boston Psychopathic Hospital.**

SATURDAY, JANUARY 28

*9-10 a. m. Joseph H. Pratt Diagnostic Hospital. Hospital case presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

SUNDAY, JANUARY 29

4 p. m. Illustrated, public, health lecture, **Faulkner Hospital**, auditorium. Recent Advances in the Treatment of Bone Injuries. Dr. Gordon M. Morrison.

4 p. m. Free public lecture, Harvard Medical School, amphitheater of Building D. Food and Drugs: Safe and unsafe. Dr. J. J. Durrett. U. S. Food and Drug Administration.

*Open to the medical profession.

JANUARY 20 — Massachusetts Italian Medical Society. Page 84, issue of January 12.

JANUARY 22 — Lecture at the Faulkner Hospital. Page 971, issue of December 15.

JANUARY 22 — Free Public Lecture, Harvard Medical School. Page 1056, issue of December 29.

JANUARY 22 — Beverly Hospital Public Health Lecture. Page 1056, issue of December 29.

JANUARY 22 - MARCH 5 — Salem Hospital Public-Health Lectures. Page 126.

JANUARY 23 — New England Heart Association. Page 83, issue of January 12.

JANUARY 24 — Harvard Medical Society. Page 126.

JANUARY 24 — Boston Medical Library. Annual meeting. Page 125.

JANUARY 24 — Arlington and Belmont medical clubs. Page 126.

JANUARY 25 — Boston Gastroenterological Society. Page 125.

JANUARY 26 — Medical clinic at the Peter Bent Brigham Hospital. Page 125.

JANUARY 26 — Winthrop Community Hospital. Page 125.

JANUARY 27 — Massachusetts Psychiatric Society. Page 125.

FEBRUARY 4, MAY 15 and 16 — American Board of Obstetrics and Gynecology. Page 451, issue of September 22. *(Application for admission to Group A examinations must be on file in the Secretary's office by March 15, instead of April 1 as previously stated.)*

FEBRUARY 7 — Robert B. Brigham Hospital. Page 125.

FEBRUARY 9 — Pentucket Association of Physicians, 8:30 p. m., Hotel Bartlett, 95 Main Street, Haverhill.

MARCH 13 — Fourth Annual Postgraduate Institute. **Page 938, issue of December 8.**

MARCH 15, MAY 15, AUGUST 5 and OCTOBER 6 — American Board of Ophthalmology. Page 126.

MARCH 27-31 — American College of Physicians. Page 36, issue of July 7.

MAY 7-15 — International Congress of Military Medicine and Pharmacy. Page 501, issue of September 29.

MAY 15-16 — American Board of Obstetrics and Gynecology, Inc. Page 937, issue of December 8.

MAY 15-19 — American Medical Association, St. Louis, Missouri.

JUNE 6, 7, 8 — Massachusetts Medical Society. Worcester.

JUNE 12-17 — Symposium on the Public-Health Significance of the Virus and Rickettsial Diseases. Page 125

JUNE 26-29 — National Tuberculosis Association. Page 936, issue of December 8.

SEPTEMBER — Boston Psychoanalytic Institute. Page 450, issue of September 22.

SEPTEMBER 11-15 — American Congress on Obstetrics and Gynecology. Page 938, issue of December 8.

SEPTEMBER 15-28 — Pan-Pacific Surgical Association. Page 863, issue of November 24.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

FEBRUARY 8 — Essex Sanatorium, Middleton. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. Edward Churchill. Subject: Surgical Treatment of Pulmonary Suppuration.

MARCH 1 — Lynn Hospital. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. John Rock. Subject: Endocrinology.

APRIL 5 — Addison Gilbert Hospital, Gloucester. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. Ethan Allan Brown. Subject: Allergy.

MAY 10 — Annual meeting. **Salem Country Club, Peabody.**

NORFOLK

JANUARY 31 — Page 126.

SUFFOLK

JANUARY 25 — Symposium on Diabetes. Page 125.

MARCH 29 — Joint meeting with New England Pediatric Society, Boston Medical Library, 8:15 p. m. Program and speakers to be announced.

APRIL 26 — Annual meeting in conjunction with Boston Medical Library, at 8:15 p. m. Election of officers. Program and speakers to be announced.

WORCESTER

FEBRUARY 8 — Worcester State Hospital.

MARCH 8 — Worcester Memorial Hospital.

APRIL 12 — Worcester Hahnemann Hospital.

MAY 10 — Worcester Country Club — Annual meeting.

With the exception of the annual meeting in May, all the meetings begin with a supper at 6:30 p. m., which is followed at 7:30 p. m. by the business and scientific sessions.

BOOKS RECEIVED FOR REVIEW

Scarlet Fever. George F. Dick and Gladys H. Dick. 149 pp. Chicago: The Year Book Publishers, Inc., 1938. $2.00.

The Journals of Bronson Alcott. Selected and edited by Odell Shepard. 558 pp. Boston: Little, Brown & Co., 1938. $5.00.

The Abnormal in Obstetrics. Comyns Berkeley, Victor Bonney and Douglas MacLeod. 525 pp. Baltimore: William Wood & Co., 1938. $6.00.

The New International Clinics. Original contributions: clinics; and evaluated reviews of current advances in the medical arts. Edited by George M. Piersol. Vol. 4, N. S. 1. 349 pp. Philadelphia, Montreal, New York: J. B. Lippincott Co., 1938. $3.00.

The Treatment of Fractures. Charles L. Scudder. Eleventh edition. 1208 pp. Philadelphia and London: W. B. Saunders Co., 1938. $12.00.

The Extra Pharmacopoeia. Martindale. Twenty-First edition. Vol. 2. 1148 pp. London: The Pharmaceutical Press, 1938. 22s. 6d.

Hygiene: Manual of public health. J. R. Currie. 324 pp. Baltimore: William Wood & Co., 1938. $5.00.

Biology for Pharmaceutical Students and Others. S. Mangham and A. R. Hockley. 613 pp. Baltimore: William Wood & Co., 1938. $6.50.

Trauma and Internal Disease: A basis for medical and legal evaluation of the etiology — pathology — clinical processes — following injury. Frank W. Spicer. 593 pp. Philadelphia, London and Montreal: J. B. Lippincott Co., 1939. $7.00.

Biographies of Child Development: The mental growth careers of eighty-four infants and children. Part 1 by Arnold Gesell. Part 2 by Catherine S. Amatruda, Burton M. Castner and Helen Thompson. 328 pp. New York and London: Paul B. Hoeber, Inc., 1939. $3.75.

BOOK REVIEWS

Interns' Handbook: A guide, especially in emergencies, for the intern and the physician in general practice. M. S. Dooley. Second edition, revised and reset. 523 pp. Philadelphia, London, Montreal: J. B. Lippincott Co., 1938. $3.00.

The first edition of this handbook was published in 1929. The *Journal* (*202*:97, 1930) reviewed it favorably, saying that the book contained a great deal of valuable information presented clearly in concentrated form.

The first part included a physician's drug list and an outline of the emergency treatment of drug poisoning. The second part outlined standard clinical procedures for

history taking, dietary, routine laboratory tests and technics for safeguarding laboratory specimens. The *Journal of the American Medical Association* (93:1173, 1929) termed it a guidebook which would enable interns and clinical clerks to adapt themselves easily to hospital routine and to acquire ability to render effective service. This seemed a fair characterization.

The second edition is a new model. It is larger than the first — 523 pages against 235; its contents have been rearranged. Now it begins with a description of the intern's relation to the hospital, tells him how to become housebroken, how to procure necropsies, what to read. The second part deals with the laboratory and is a handy compendium of clinical pathology. The third section concerns medicine; the fourth, surgery; and the fifth, therapy, where once more the emergency treatment of drug poisoning is included. The sixth section deals with nursing, wherein are described simple methods for improvising backrests or cradles, for turning a helpless patient and for bedmaking; all taken as a matter of course in hospital life but which are not so simple when young Lydgate goes alone to his first sick patient's home with no equipment but his own common sense and the recollection of how things were done when he was an intern.

All this information once again is well printed in legible type, is presented in clear, concentrated form, so arranged that quick reference is possible, and is compressed into a small-sized volume which easily fits into one's bag or pocket. The *Journal* is glad to repeat: the book is one of the best of its kind and should be useful to practitioners as well as to interns.

Meningiomas: Their classification, regional behaviour, life history and surgical end results. Harvey Cushing. 785 pp. Springfield, Illinois: Charles C Thomas, 1938. $15.00.

It has long been hoped that Dr. Cushing would, now that he has retired from the active practice of surgery, review his experiences with various types of brain tumors and record not only the results but his methods of handling these dangerous and destructive lesions. Away from the two hospitals where his work was done and giving much of his time to literary work and the cataloguing of his large library of historical works, many must have thought that no effort on his part would result in a book such as he has produced on meningiomas. He not only brought to his desk in New Haven the records by photostat of all his patients, but he also followed them as carefully as if each were still calling at his office. A total of 313 cases, each followed to death or, if living, to the present time, with accurate notes of the conditions at postmortem or reports on the clinical conditions of all living patients, is presented in this monograph. At once it may be said that no surgeon has ever had such a complete series of case-histories to deal with, for no surgeon up to Dr. Cushing's time ever followed all his cases so persistently. Great credit for this should go also to the junior author, Dr. Eisenhardt, who has shown as much zeal in following patients as in working out the details of the pathology of meningiomas.

The series of cases, operated on from October, 1903, to October, 1932, constitutes the bulk of the volume. Each case-history is given in detail with a wealth of illustrations — roentgenograms, operative sketches, photographs of tumors, photographs of patients and pictures showing the microscopic appearance of the lesions. In addition, there are chapters on pathology, tumor incidence, the types of tumors according to their location, diagnosis and operative technic and a complete bibliography and index. The introductions to many chapters contain historical material, often illustrated. An unusual feature is the recording of the actual name of each patient and the giving over of separate chapters to the "Case of Timothy Donovan" and the "Case of Dorothy Russell," two brave patients, each with recurrent meningiomas requiring repeated operations. With humanity seldom found in textbooks and with true literary skill, Dr. Cushing has depicted the medical lives of two heroes, both sure to have a permanent place in the annals of medical history.

In regard to meningiomas in general the following points are brought out: solitary tumors have favorite loci of origin; tumors of each locus behave in much the same way; certain meningiomas tend to recur; 172 of the 313 patients were alive in 1937 — 132 with a period of five years or more after operation; the survival period may be twenty or more years; case mortality was greatly reduced as the result of electrosurgical methods introduced in 1927; meningiomas may be classified according to nine pathological types, with variants; the types often described as epitheliomatous or sarcomatous have as favorable a prognosis as the "dural endotheliomas" or the fibroblastic tumors. These and many other points are clearly brought out.

A word should be said in regard to the publisher and printer. The illustrations, skillfully placed on each page, are remarkably clear, the tables finely arranged and the spacing about the figures carefully placed. Each page has a pleasing appearance as well as boldly bringing out the illustrative points by both pictures and variations in type. In a 785-page book with 685 illustrations and numerous charts, only one unimportant error was found in a fairly complete reading of the text.

The reviewer is left with the impression that a book of more than ordinary value has come to his hand. Every page shows the master surgeon and the literary ability of the author. To be sure, no one else had so much knowledge of this type of tumor as did the author, but, on the other hand, who but Dr. Cushing could write so clearly, so frankly of his mistakes and so charmingly about his patients? Surgically, this is a book of the first importance; historically, it is a classic.

The Home Book of Medicine. David Polowe. 581 pp. New York: Greenberg, 1938. $2.75.

The purpose of the author of this book is to have it included in the family library for the instruction of those who may be responsible for the health of the household.

With this in view a brief description of the construction of the human body is presented, together with the essential facts concerning the functions of the important organs and systems. After a discussion of the etiology and prevention of disease, advice is given about the selection of a doctor and what should be done under certain circumstances before the patient is under professional supervision.

The chapters next in order are devoted to nursing and the care of convalescent patients and to a consideration of chronic diseases. The remaining pages — over half the book — deal with the symptomatology, diagnosis and treatment of diseases, accidents and other emergencies, approved diet lists and co-ordinate subjects.

The book is well written and in a concise fashion covers most of the common phases of illness, but the question as to the wisdom of trying to teach non-medical persons so much of medicine seems pertinent because some people may be led to feel that the employment of a doctor in a given case is not required, with disastrous results.